Policy Number	**RX501.142**
Policy Effective Date	**09/15/2024**
Policy End Date	**12/31/2025**

Inclisiran

Table of Contents

Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Inclisiran (Leqvio®) **may be considered medically necessary** when the following criteria are met:

- Adults with a diagnosis of heterozygous familial hypercholesterolemia (HeFH) or primary hyperlipidemia with high risk of cardiovascular (CV) disease (e.g., diabetes, hypertension); AND
- Member has a current LDL-C $\geq$ 70 mg/dl while taking a maximally tolerated dose of statin with or without other lipid modifying therapy; AND
- Member will continue to receive concomitant statin therapy if no documented contraindication or intolerance; AND
- Will **NOT** use inclisiran concurrently with other PCSK9 (proprotein convertase subtilisin kexin type 9) therapies (e.g., evolocumab [Repatha] and alirocumab [Praluent]).

Inclisiran (Leqvio®) **is considered experimental, investigational and/or unproven** for all other indications.

NOTE 1: Inclisiran (Leqvio®) is a subcutaneous injection and should be administered by a healthcare professional.

Policy Guidelines

None.

Description

Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) is an inherited disorder characterized by markedly elevated low-density lipoprotein (LDL) levels, physical exam signs of cholesterol deposition, and premature cardiovascular disease. Familial hypercholesterolemia can be categorized as homozygous or heterozygous FH. Homozygous FH is an extremely rare disorder that arises from biallelic variants in a single gene, and the disorder has a prevalence of between 1:160000 and 1:1000000. (1) Individuals with homozygous FH have extreme elevations of LDL, develop coronary artery disease (CAD) in the second or third decade, and are generally diagnosed easily.

Heterozygous FH is more common, with an estimated prevalence between 1 in 200 to 1 in 500 individuals. (2, 3, 4) Some populations, such as Ashkenazi Jews and South Africans, have a higher prevalence of up to 1 in 100. (2) For affected individuals, the burden of illness is high.

Patients with FH and increased LDL cholesterol (>190 mg/dL) have a 3 times higher risk of CAD than those with increased LDL cholesterol alone. (5) The average age for presentation with CAD is in the fourth decade for men and the fifth decade for women, and there is a 30% to 50% increase in risk for men and women in the fifth and sixth decades, respectively. (3) Increased risk of CAD is associated with a higher rate of death associated with cardiovascular causes in patients with homozygous and heterozygous FH. (6)

Diagnosis

The diagnosis of FH relies on elevated LDL levels in conjunction with a family history of premature CAD and physical exam signs of cholesterol deposition. There is wide variability in cholesterol levels for patients with FH, and considerable overlap in levels between patients with FH and patients with non-FH. Physical exam findings can include tendinous xanthomas, xanthelasma, and corneal arcus, but these are not often helpful in making a diagnosis. Xanthelasma and corneal arcus are common in the elderly population and therefore not specific. Tendinous xanthomas are relatively specific for FH but are not sensitive findings. They occur mostly in patients with higher LDL levels and treatment with statins likely delays or prevents the development of xanthomas.

Because of the variable cholesterol levels, and the low sensitivity of physical exam findings, there are a considerable number of patients in whom the diagnosis is uncertain. For these individuals, there are several formal diagnostic tools for determining the likelihood of FH. (7, 8)

Simon-Broome Register Criteria

Using these criteria, a definite diagnosis of FH is made based on total cholesterol that is greater than 290 mg/dL in adults (or LDL >190 mg/dL) together with tendinous xanthoma in the individual or a first-degree relative. A definite diagnosis can also be made using cholesterol levels and a positive genetic test. Probable FH is diagnosed by cholesterol levels and either a family history of premature myocardial infarction or a family history of total cholesterol 290 mg/dL or higher in a first- or a second-degree relative. See Table 1.

Table 1. Simon Broome Familial Hypercholesterolemia Register Diagnostic Criterial for Familial Hypercholesterolemia (FH) (9)

Criteria	Description
a	Total cholesterol concentration above 7.5 mmol/liter (290 mg/dL) in adults or a total cholesterol concentration above 6.7 mmol/liter (259 mg/dL) in children aged less than 16 years, or
	Low-density lipoprotein cholesterol concentration above 4.9 mmol/liter (189 mg/dL) in adults or above 4.0 mmol/liter (155 mg/dL) in children
b	Tendinous xanthomata in the patient or a first-degree relative
c	DNA-based evidence of mutation in the LDLR, PCSK9, or APOB gene
d	Family history of myocardial infarction before age 50 years in a second-degree relative or before age 60 years in a first-degree relative

e	Family history of raised total cholesterol concentration above 7.5 mmol/liter (290 mg/dL) in a first- or second-degree relative
A "definite" FH diagnosis requires either criteria *a* and *b*, or criterion *c*. A "probable" FH diagnosis requires either criteria *a* and *d,* or criteria *a* and *e*.	

LDLR: low density lipoprotein receptor Apo B: apolipoprotein B; PCSK9: Proprotein convertase subtilisin/kexin type 9.

Dutch Lipid Clinic Network Criteria

This tool assigns points for family history, CAD in the individual, physical exam signs of cholesterol deposition, LDL levels, and results of genetic testing. The diagnosis of definite FH is made when the score is higher than 8 and probable FH when the score is 6 to 8. The diagnosis can be made with or without genetic testing. A positive genetic test is given 8 points, which is the highest for any criterion and indicates that a positive genetic test alone is sufficient to make a definitive diagnosis. See Table 2.

Table 2. Dutch Lipid Clinic Network Diagnostic Criteria for Familial Hypercholesterolemia (9)

Criteria	Points
1) Family History	
• First-degree relative with known premature (men: <55 years; women: <60 years) coronary or vascular disease; or • First-degree relative with known LDL-C above the 95th percentile	1
• First-degree relative with tendinous xanthomata and/or arcus cornealis; or • Children <18 years of age with LDL-C above the 95th percentile	2
2) Clinical History	
• Patient with premature (men: <55 years; women: <60 years) coronary artery disease	2
• Patient with premature (men: <55 years; women <60 years) cerebral or peripheral vascular disease	1
3) Physical Examination	
• Tendinous xanthomata	6
• Arcus cornealis before age 45 years	4
4) LDL-C Levels	
• LCL-C ≥8.5 mmol/L (325 mg/dL)	8
• LDL-C 6.5 to 8.4 mmol/L (251-325 mg/dL)	5
• LDL-C 5 to 6.4 mmol/L (191-250 mg/dL)	3
• LDL-C 4 to 4.9 mmol/L (155-190 mg/dL)	1
5) DNA Analysis	
• Functional mutation in the LDLR, apoB, or PCSK9 gene	8
Diagnosis is based on the total number of points obtained, using one score per group	
• Definite familial hypercholesterolemia	>8
• Probable familial hypercholesterolemia	6-8

• Possible familial hypercholesterolemia	3-5
• Unlikely familial hypercholesterolemia	≤3

LDL-C: low density lipoprotein cholesterol; LDLR: low density lipoprotein receptor Apo B: apolipoprotein B; PCSK9: Proprotein convertase subtilisin/kexin type 9.

Treatment

Treatment of FH is generally similar to that for non-FH and is based on LDL levels. Treatment may differ in that the approach to treating FH is more aggressive (i.e., treatment may be initiated sooner, and a higher intensity medication regimen may be used). In adults, there are no specific treatment guidelines that indicate treatment for FH differs from the standard treatment of hypercholesterolemia. There may be more differences in children, for whom the presence of a pathogenic variant may impact the timing of starting medications. As with other forms of hypercholesterolemia, statins are the mainstay of treatment for FH. However, because of the degree of elevated LDL in many patients with FH, statins will not be sufficient to achieve target lipid levels. Additional medications can be used in these patients.

Atherosclerotic Cardiovascular Disease

Atherosclerotic cardiovascular disease (ASCVD) is common in the general population, affecting many adults over the age of 60 years. It includes four major areas:

- Coronary heart disease (CHD) manifested by fatal or nonfatal myocardial infarction (MI), angina pectoris, and/or heart failure.
- Cerebrovascular disease manifested by fatal or nonfatal stroke or transient ischemic attack.
- Peripheral artery disease manifested by intermittent claudication and critical limb ischemia.
- Aortic atherosclerosis and thoracic or abdominal aortic aneurysm.

Risk factors for ASCVD include hypertension; cigarette smoking; diabetes mellitus (DM); hyperlipidemia including known familial hyperlipidemia or an individual history of elevated total cholesterol or low-density lipoprotein (LDL) cholesterol; premature family history of ASCVD; and obesity. For individuals ≥20 years of age, a baseline lipid profile is generally obtained. If severely elevated LDL cholesterol ≥190 mg/dL (≥4.9 mmol/L) is present, then the patient will be treated aggressively with recommended lifestyle modifications and lipid-lowering medications.

Treatment

Treatment for familial hypercholesterolemia (FH) includes counseling for lifestyle changes that may decrease LDL-C levels as well as other cardiovascular risks. Counseling should include dietary modification, physical activity, and weight loss in obese individuals. Aspirin may be appropriate as these individuals may be at a high risk of cardiovascular disease risk, especially for patients with clinical atherosclerotic cardiovascular disease (ASCVD), and men >55 years of age who have multiple coronary heart disease risk factors.

Statin therapy is also recommended for individuals at high or intermediate risk. The American College of Cardiology/American Heart Association (ACC/AHA) defines cardiovascular risk categories as “high” (10-year risk of cardiovascular events ≥20%), “intermediate” (10-year risk of cardiovascular events ≥7.5% to <20%), and “borderline” (10-year risk of cardiovascular

events 5% to <7.5%). It recommends initiation of statin therapy in persons at "intermediate" or "high" risk, and a risk discussion for persons at "borderline" risk. Table 3 provides examples of high, moderate, and low-intensity statin therapy.

Table 3. High-, Moderate-, and Low-Intensity Statin Therapy (10, 11)

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL-C, on average, by approximately ≥50%	Daily dose lowers LDL-C, on average, by approximately 30% to <50%	Daily dose lowers LDL-C, on average, by <30%
Atorvastatin 40–80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20–40 mg Pravastatin 40-80 mg Lovastatin 40-80 mg Fluvastatin 80 mg Pitavastatin 1-4 mg	Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg

LDL-C: low-density lipoprotein cholesterol; mg: milligrams

Inclisiran

Inclisiran sodium is a small interfering RNA (siRNA) directed to PCSK9 (proprotein convertase subtilisin kexin type 9) protein. siRNA molecules use the natural pathway of selective gene expression silencing. Inclisiran inhibits the expression of PCSK9 by binding specifically to the mRNA precursor of PCSK9 protein and causing its degradation.

Regulatory Status

Inclisiran (Leqvio®) was granted approval by the U.S. Food and Drug Administration (FDA) in 2021. It 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). Leqvio is a subcutaneous injection and should be administered by a healthcare professional. (12)

Rationale

This medical policy was developed in 2022 and is based on the clinical studies provided to the U.S. Food and Drug Administration (FDA) for approval.

Leqvio (12)

The efficacy of Leqvio was investigated in three randomized, double-blind, placebo-controlled trials that enrolled 3,660 adults with heterozygous familial hypercholesterolemia (HeFH), clinical atherosclerotic cardiovascular disease (ASCVD), or increased risk for ASCVD, who were taking maximally tolerated statin therapy and who required additional low-density lipoprotein

cholesterol (LDL-C) lowering. Demographics and baseline disease characteristics were balanced between the treatment arms in all trials.

Primary Hyperlipidemia

Study 1 (ORION-10, NCT03399370) was a multicenter, double-blind, randomized, placebo-controlled 18-month trial in which 1561 patients with ASCVD were randomized 1:1 to receive subcutaneous injections of either Leqvio 284 mg (n = 781) or placebo (n = 780) on Day 1, Day 90, Day 270, and at Day 450. Patients were taking a maximally tolerated dose of statin with or without other lipid modifying therapy and required additional LDL-C reduction. Patients were stratified by current use of statins or other lipid-modifying therapies. Patients taking proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors were excluded from the trial.

The mean age at baseline was 66 years (range: 35 to 90 years), 60% were ≥ 65 years old, 31% were women, 86% were White, 13% were Black, 1% were Asian and 14% identified as Hispanic or Latino ethnicity. Forty-five percent (45%) of patients had diabetes at baseline. The mean baseline LDL-C was 105 mg/dL. At the time of randomization, 89% of patients were receiving statin therapy and 69% were receiving high-intensity statin therapy.

The primary efficacy outcome measure in Study 1 was the percent change from baseline to Day 510 in LDL-C. The difference between the Leqvio and placebo groups in mean percentage change in LDL-C from baseline to Day 510 was -52% (95% CI: -56%, -49%; $p < 0.0001$). For additional results, see Table 4 and Figure 1.

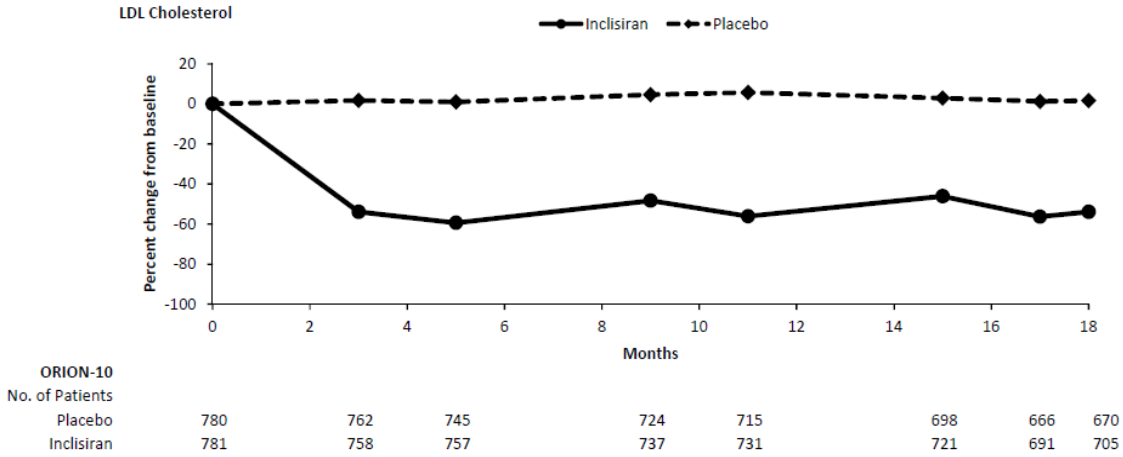
Table 4. Changes in Lipid Parameters in Patients with ASCVD on Maximally Tolerated Statin Therapy (Mean % Change from Baseline to Day 510 in Study 1)

Treatment Group	LDL-C	Total Cholesterol	Non-HDL-C	ApoB
Day 510 (mean percentage change from baseline)[a]				
Placebo (n=780)	1	0	0	-2
Leqvio (n=781)	-51	-34	-47	-45
Difference from placebo (LS mean) (95% CI)	-52 (-56, -49)	-33 (-35, -31)	-47 (-50, -44)	-43 (-46, -41)

ASCVD: clinical atherosclerotic cardiovascular disease; ApoB: apolipoprotein B; CI: confidence interval; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

[a]11.5% of subjects on Leqvio and 14.6% of subjects on placebo had missing LDL-C data at primary endpoint (Day 510). Missing data were imputed using a modified control-based multiple imputation to account for treatment adherence. Percent change from baseline in LDL-C was analyzed using analysis of covariance (ANCOVA) with fixed effect for treatment group and baseline LDL-C as a covariate. Other endpoints were analyzed using a mixed-effect model for repeated measure (MMRM) with fixed effects for treatment group, visit, interaction between treatment and visit, and baseline value. Missing data were imputed using a control-based pattern-mixture model approach.

Figure 1: Mean Percent Change from Baseline in LDL-C Over 18 Months in Patients with ASCVD on Maximally Tolerated Statin Therapy (Study 1)



Study 2 (ORION-11, NCT03400800) was a multicenter, double-blind, randomized, placebo-controlled 18-month trial in which 1,617 adults with ASCVD or increased risk for ASCVD were randomized 1:1 to receive subcutaneous injections of either Leqvio 284 mg (n = 810) or placebo (n = 807) on Day 1, Day 90, Day 270, and Day 450. Patients were taking a maximally tolerated dose of statin with or without other lipid modifying therapy and required additional LDL-C reduction. Patients were stratified by country and by current use of statins or other lipid-modifying therapies. Patients taking PCSK9 inhibitors were excluded from the trial.

The mean age at baseline was 65 years (range: 20 to 88 years), 55% were ≥ 65 years old, 28% were women, 98% were White, 1% were Black or African American, < 1% were Asian, and 1% identified as Hispanic or Latino ethnicity. Thirty-five percent (35%) of patients had diabetes at baseline. The mean baseline LDL-C was 105 mg/dL. At the time of randomization, 95% of patients were receiving statin therapy and 78% were receiving high-intensity statin therapy.

The primary efficacy outcome measure in Study 2 was the percent change from baseline to Day 510 in LDL-C. The difference between the Leqvio and placebo groups in mean percentage change in LDL-C from baseline to Day 510 was -50% (95% CI: -53%, -47%; p < 0.0001). For additional results, see Table 5 and Figure 2.

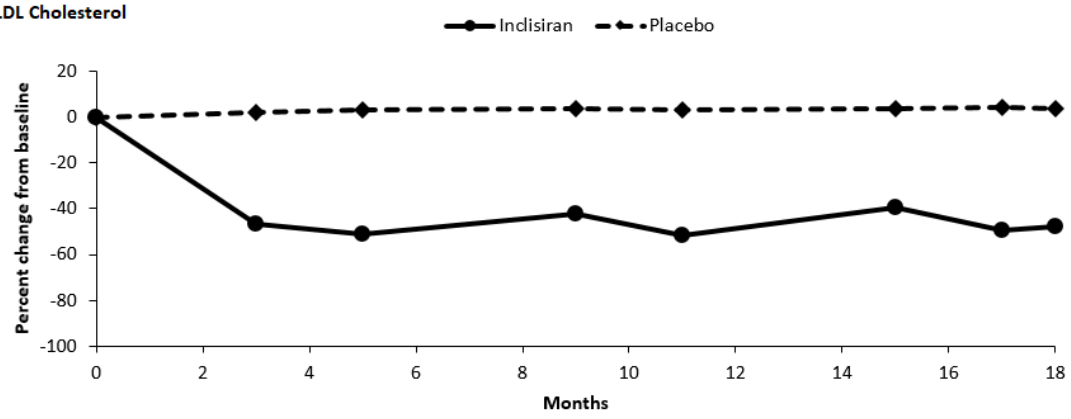
Table 5. Changes in Lipid Parameters in Patients with ASCVD on Maximally Tolerated Statin Therapy (Mean % Change from Baseline to Day 510 in Study 2)

Treatment Group	LDL-C	Total Cholesterol	Non-HDL-C	ApoB
Day 510 (mean percentage change from baseline)[a]				
Placebo (n=807)	4	2	2	1
Leqvio (n=810)	-46	-28	-41	-38

Difference from placebo (LS mean) (95% CI)	-50 (-53, -47)	-30 (-32, -28)	-43 (-46, -41)	-39 (-41, -37)

ASCVD: clinical atherosclerotic cardiovascular disease; ApoB: apolipoprotein B; CI: confidence interval; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.
[a]10.6% of subjects on Leqvio and 8.4% of subjects on placebo had missing LDL-C data at primary endpoint (Day 510). Missing data were imputed using a modified control-based multiple imputation to account for treatment adherence. Percent change from baseline in LDL-C was analyzed using analysis of covariance (ANCOVA) with fixed effect for treatment group and baseline LDL-C as a covariate. Other endpoints were analyzed using mixed-effect model for repeated measure (MMRM) with fixed effects for treatment group, visit, interaction between treatment and visit, and baseline value. Missing data were imputed using a control-based pattern-mixture model approach.

Figure 2. Mean Percent Change from Baseline in LDL-C Over 18 Months in Patients with ASCVD on Maximally Tolerated Statin Therapy (Study 2)



ORION-11								
No. of Patients								
Placebo	807	797	785	774	773	764	739	749
Inclisiran	810	790	796	778	773	768	724	742

In a pooled analysis of Study 1 and Study 2, the observed treatment effect was similar across predefined subgroups, such as sex, age, race, disease characteristics, geographic regions, presence of diabetes, body mass index, baseline LDL-C levels, and intensity of statin treatment.

Low Density Lipoprotein Cholesterol (LDL-C) Reduction in Patients with Heterozygous Familial Hypercholesterolemia (HeFH)

Study 3 (ORION-9, NCT03397121) was a multicenter, double-blind, randomized, placebo-controlled 18-month trial in which 482 patients with HeFH were randomized 1:1 to receive subcutaneous injections of either Leqvio 284 mg (n = 242) or placebo (n = 240) on Day 1, Day 90, Day 270, and at Day 450. Patients with HeFH were taking a maximally tolerated dose of statin with or without other lipid modifying therapy and required additional LDL-C reduction. The diagnosis of HeFH was made either by genotyping or clinical criteria using either the Simon Broome or WHO/Dutch Lipid Network criteria. Patients were stratified by country and by current use of statins or other lipid-modifying therapies. Patients taking PCSK9 inhibitors were excluded from the trial.

The mean age at baseline was 55 years (range: 21 to 80 years), 22% were ≥ 65 years old, 53% were women, 94% were White, 3% were Black or African American, 3% were Asian and 3% identified as Hispanic or Latino ethnicity. Ten percent (10%) of patients had diabetes at baseline. The mean baseline LDL-C was 153 mg/dL. At the time of randomization, 90% of patients were receiving statin therapy and 74% were receiving high-intensity statin therapy. Fifty-two percent (52%) of patients were treated with ezetimibe. The most commonly administered statins were atorvastatin and rosuvastatin.

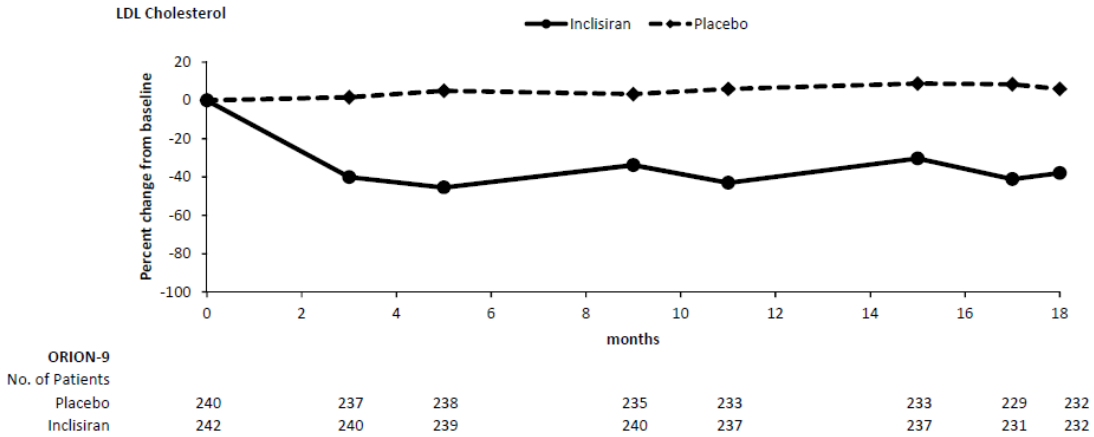
The primary efficacy outcome measure in Study 3 was the percent change from baseline to Day 510 in LDL-C. The difference between the Leqvio and placebo groups in mean percentage change in LDL-C from baseline to Day 510 was -48% (95% CI: -54%, -42%; $p < 0.0001$). For additional results, see Table 5 and Figure 3.

Table 6. Changes in Lipid Parameters in Patients with HeFH on Maximally Tolerated Statin Therapy (Mean % Change in Baseline to Day 510 in Study 3)

Treatment Group	LDL-C	Total Cholesterol	Non-HDL-C	ApoB
Day 510 (mean percentage change from baseline)[a]				
Placebo (n=240)	8	7	7	3
Leqvio (n=242)	-40	-25	-35	-33
Difference from placebo (LS mean) (95% CI)	-48 (-54, -42)	-32 (-36, -28)	-42 (-47, -37)	-36 (-40, -32)

HeFH: heterozygous familial hypercholesterolemia; ApoB: apolipoprotein B; CI: confidence interval; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.
[a]4.5% of subjects on Leqvio and 4.6% of subjects on placebo had missing LDL-C data at primary endpoint (Day 510). Missing data were imputed using a modified control-based multiple imputation to account for treatment adherence. Percent change from baseline in LDL-C was analyzed using analysis of covariance (ANCOVA) with fixed effect for treatment group and baseline LDL-C as a covariate. Other endpoints were analyzed using mixed-effect model for repeated measure (MMRM) with fixed effects for treatment group, visit, interaction between treatment and visit, and baseline value as a covariate. Missing data were imputed using a control-based pattern-mixture model approach.

Figure 3. Mean Percent Change from Baseline in LDL-C Over 18 Months in Patients with HeFH on Maximally Tolerated Statin Therapy (Study 3)



Summary of Evidence

Based on the clinical studies provided to the U.S. Food and Drug Administration, inclisiran (Leqvio®) may be medically necessary as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH) to reduce low-density lipoprotein cholesterol (LDL-C). Inclisiran (Leqvio®) is considered experimental, investigational and/or unproven for all other indications.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J1306

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

References

1. Youngblom E, Knowles JW. Familial Hypercholesterolemia. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews(R). Seattle, WA: University of Washington; 2014.
2. Bouhairie VE, Goldberg AC. Familial Hypercholesterolemia. Endocrinol Metab Clin North Am. Mar 2016; 45(1):1-16. PMID 26892994

3. Patel RS, Scopelliti EM, Savelloni J. Therapeutic management of familial hypercholesterolemia: current and emerging drug therapies. Pharmacotherapy. Dec 2015; 35(12):1189-1203. PMID 26684558
4. Hu P, Dharmayat KI, Stevens CAT, et al. Prevalence of familial hypercholesterolemia among the general population and patients with atherosclerotic cardiovascular disease: a systematic review and meta-analysis. Circulation. Jun 02 2020; 141(22):1742-1759. PMID 32468833
5. Khera AV, Won HH, Peloso GM, et al. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. J Am Coll Cardiol. Jun 07 2016; 67(22):2578-2589. PMID 27050191
6. Mundal L, Igland J, Ose L, et al. Cardiovascular disease mortality in patients with genetically verified familial hypercholesterolemia in Norway during 1992-2013. Eur J Prev Cardiol. Jan 2017; 24(2):137-144. PMID 27794106
7. McGowan MP, Hosseini Dehkordi SH, Moriarty PM, et al. Diagnosis and treatment of heterozygous familial hypercholesterolemia. J Am Heart Assoc. Dec 17 2019; 8(24):e013225. PMID 31838973
8. Bilen O, Pokharel Y, Ballantyne CM. Genetic testing in hyperlipidemia. Endocrinol Metab Clin North Am. Mar 2016; 45(1):129-140. PMID 26893002
9. Rosenson RS, Durrington P. Familial hypercholesterolemia in adults: Overview. In: UpToDate, Freeman MW (Ed), UpToDate, Waltham, MA. Available at: <http://www.uptodate.com> (accessed May 1, 2023).
10. Reiter-Brennan C, Osei AD, Iftekhar Uddin SM, et al. ACC/AHA lipid guidelines: Personalized care to prevent cardiovascular disease. Cleve Clin J Medicine. 2020 Apr; 87(4):231-239. PMID 32238379
11. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019 Jun 25; 73(24):3168-3209. PMID 30423391
12. U.S. Food and Drug Administration, Drugs@FDA. Highlights of prescribing information: Leqvio® (Inclisiran) (July 2023). Available at: <https://www.accessdata.fda.gov> (accessed December 26, 2023).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
09/15/2024	Reviewed. No changes.
03/01/2024	Document updated with literature review. The following change was made to Coverage: Changed Adults with a diagnosis of heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD); to Adults with a diagnosis of heterozygous familial hypercholesterolemia (HeFH) or primary hyperlipidemia with high risk of cardiovascular (CV) disease (e.g., diabetes, hypertension). References updated; no new references added.
10/01/2023	Document updated with literature review. The following changes were made to Coverage: 1) Updated language specific to LDL-C level, and 2) Added criteria for continued concomitant statin therapy. Added reference 1-8 and 11.
07/01/2022	New medical document. Inclisiran (Leqvio®) may be medically necessary when the following criteria are met: Adults with a diagnosis of heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD); AND Member is on a maximally tolerated dose of statin with or without other lipid modifying therapy; AND Member requires additional reduction of low-density lipoprotein cholesterol (LDL-C); AND Will NOT use inclisiran concurrently with other PCSK9 (proprotein convertase subtilisin kexin type 9) therapies (e.g., evolocumab [Repatha] and alirocumab [Praluent]). Inclisiran (Leqvio®) is considered experimental, investigational and/or unproven for all other indications.