CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

214012Orig1s009

Trade Name:	LEQVIO
Generic or Proper Name:	inclisiran
Sponsor:	Novartis Pharmaceuticals Corporation
Approval Date:	July 7, 2023
Indication:	LEQVIO is a small interfering RNA (siRNA) directed to proprotein convertase subtilisin kexin type 9 (PCSK9) mRNA 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).

CENTER FOR DRUG EVALUATION AND RESEARCH

214012Orig1s009

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

NDA 214012/S-009

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Mona Fassihi, PharmD, MS
Senior Global Program Regulatory Manager, Regulatory Affairs
One Health Plaza
Building 337
East Hanover, NJ 07936-1080

Dear Dr. Fassihi:

Please refer to your supplemental new drug application (sNDA) dated and received May 25, 2023, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Leqvio (inclisiran) injection.

This Prior Approval sNDA provides for revisions to Section 1 *Indications and Usage,* the removal of the Limitations of Use statement, and other formatting and minor changes in the Leqvio Prescribing Information to conform to current labeling practices as requested in our May 5, 2023, Prior Approval Supplement Request letter.

APPROVAL & LABELING

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling with minor editorial revisions listed below and reflected in the enclosed labeling.

- Recent Major Changes and Revision dates updated in the Highlights of Prescribing Information to reflect sNDA approval.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

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[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.[6]

If you have any questions, call Ron Picking, Regulatory Project Manager, at 240-402-3211.

Sincerely,

{See appended electronic signature page}

John Sharretts, M.D.
Director
Division of Diabetes, Lipid Disorders, and Obesity
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:

- Content of Labeling
  - Prescribing Information

[6] https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOHN M SHARRETTS
07/07/2023 02:48:56 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214012Orig1s009

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LEQVIO safely and effectively. See full prescribing information for LEQVIO.

LEQVIO® (inclisiran) injection, for subcutaneous use
Initial U.S. Approval: 2021

----------RECENT MAJOR CHANGES----------
Indications and Usage (1) 7/2023

----------INDICATIONS AND USAGE----------
LEQVIO is a small interfering RNA (siRNA) directed to proprotein convertase subtilisin kexin type 9 (PCSK9) mRNA indicated as an adjunct to diet and statin therapy for the treatment of adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce low-density lipoprotein cholesterol (LDL-C). (1)

----------DOSAGE AND ADMINISTRATION----------
- The recommended dosage of LEQVIO, in combination with statin therapy, is 284 mg administered as a single subcutaneous injection initially, again at 3 months, and then every 6 months. (2.1)
- LEQVIO should be administered by a healthcare professional. (2.2)
- Inject LEQVIO subcutaneously into the abdomen, upper arm, or thigh. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 284 mg/1.5 mL (189 mg/mL) in a single-dose prefilled syringe. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------ADVERSE REACTIONS----------
Common adverse reactions in clinical trials (≥ 3%): injection site reaction, arthralgia, and bronchitis. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 7/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

- The recommended dosage of LEQVIO, 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 LEQVIO 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 LEQVIO initially, again at 3 months, and then every 6 months.
- Assess LDL-C when clinically indicated. The LDL-lowering effect of LEQVIO may be measured as early as 30 days after initiation and anytime thereafter without regard to timing of the dose.

2.2 Important Administration Instructions

- LEQVIO should be administered by a healthcare professional.
- Inject LEQVIO 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.
- Inspect LEQVIO visually before use. It should appear clear and colorless to pale yellow. Do not use if particulate matter or discoloration is seen.

3 DOSAGE FORMS AND STRENGTHS

Injection: 284 mg/1.5 mL (189 mg/mL) of inclisiran as a clear, and colorless to pale yellow solution in a single-dose prefilled syringe.

4 CONTRAINDICATIONS

None.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in Table 1 are derived from 3 placebo-controlled trials that included 1,833 patients treated with LEQVIO, including 1,682 exposed for 18 months (median treatment duration of 77 weeks) *[see Clinical Studies (14)]*. The mean age of the population was 64 years, 32% of the population were women, 92% were White, 6% were Black or African American, 1% were Asian, and < 1% were other races; 6% identified as Hispanic or

Latino ethnicity. At baseline, 12% of patients had a diagnosis of HeFH and 85% had clinical atherosclerotic cardiovascular disease (ASCVD).

Adverse reactions reported in at least 3% of LEQVIO-treated patients, and more frequently than in placebo-treated patients, are shown in Table 1.

Table 1: Adverse Reactions Occurring in Greater Than or Equal to 3% of LEQVIO-treated Patients and More Frequently than with Placebo (Studies 1, 2, and 3)

Adverse Reactions	Placebo (N = 1,822) %	LEQVIO (N = 1,833) %
Injection site reaction†	2	8
Arthralgia	4	5
Bronchitis	3	4

†includes related terms such as: injection site pain, erythema and rash

Adverse reactions led to discontinuation of treatment in 2.5% of patients treated with LEQVIO and 1.9% of patients treated with placebo. The most common adverse reactions leading to treatment discontinuation in patients treated with LEQVIO were injection site reactions (0.2% versus 0% for LEQVIO and placebo, respectively).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Discontinue LEQVIO when pregnancy is recognized. Alternatively, consider the ongoing therapeutic needs of the individual patient. Inclisiran increases LDL-C uptake and lowers LDL-C levels in the circulation, thus decreasing cholesterol and possibly other biologically active substances derived from cholesterol; therefore, LEQVIO may cause fetal harm when administered to pregnant patients based on the mechanism of action *[see Clinical Pharmacology (12.1)]*. In addition, treatment of hyperlipidemia is not generally necessary during pregnancy. 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.

There are no available data on the use of LEQVIO in pregnant patients to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.

In animal reproduction studies, no adverse developmental effects were observed in rats and rabbits with subcutaneous administration of inclisiran during organogenesis at doses up to 5 to 10 times the maximum recommended human dose (MRHD) based on body surface area (BSA) comparison *(see Data)*. No adverse developmental outcomes were observed in offspring of rats administered inclisiran from organogenesis through lactation at 5 times the MRHD based on BSA comparison *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%–4% and 15%–20%, respectively.

Data

Animal Data

In embryo-fetal development studies conducted in Sprague-Dawley rats and New Zealand White rabbits, inclisiran was administered by subcutaneous injection at dose levels of 50, 100, and 150 mg/kg once daily during organogenesis (rats: Gestation Days 6 to 17; rabbits: Gestation Days 7 to 19). There was no evidence of

embryo-fetal toxicity or teratogenicity at doses up to 5 and 10 times, respectively, the MRHD based on BSA comparison/dose. Inclisiran crosses the placenta and was detected in rat fetal plasma at concentrations that were 65 to 154 times lower than maternal levels.

In a pre- and postnatal development study conducted in Sprague-Dawley rats, inclisiran was administered once daily by subcutaneous injection at levels of 50, 100, and 150 mg/kg from Gestation Day 6 through Lactation Day 20. Inclisiran was well-tolerated in maternal rats, with no evidence of maternal toxicity and no effects on maternal performance. There were no effects on the development of the F1 generation, including survival, growth, physical and reflexological development, behavior, and reproductive performance at doses up to 5 times the MRHD, based on BSA comparison/dose.

8.2 Lactation

Risk Summary

There is no information on the presence of inclisiran in human milk, the effects on the breastfed infant, or the effects on milk production. Inclisiran was present in the milk of lactating rats in all dose groups. When a drug is present in animal milk, it is likely that the drug will be present in human milk *(see Data)*. Oligonucleotide-based products typically have poor oral bioavailability; therefore, it is considered unlikely that low levels of inclisiran present in milk will adversely impact an infant's development during lactation. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LEQVIO and any potential adverse effects on the breastfed infant from LEQVIO or from the underlying maternal condition.

Data

In lactating rats, inclisiran was detected in milk at mean maternal plasma:milk ratios that ranged between 0.361 and 1.79. However, there is no evidence of systemic absorption in the suckling rat neonates.

8.4 Pediatric Use

The safety and effectiveness of LEQVIO have not been established in pediatric patients.

8.5 Geriatric Use

Of the 1,833 patients treated with LEQVIO in clinical studies, 981 (54%) patients were 65 years of age and older, while 239 (13%) patients were 75 years of age and older. No overall differences in safety or effectiveness were observed between patients 65 years of age and older and younger adult patients.

8.6 Renal Impairment

No dose adjustments are necessary for patients with mild, moderate, or severe renal impairment *[see Clinical Pharmacology (12.3)]*. LEQVIO has not been studied in patients with end stage renal disease *[see Clinical Pharmacology (12.3)]*.

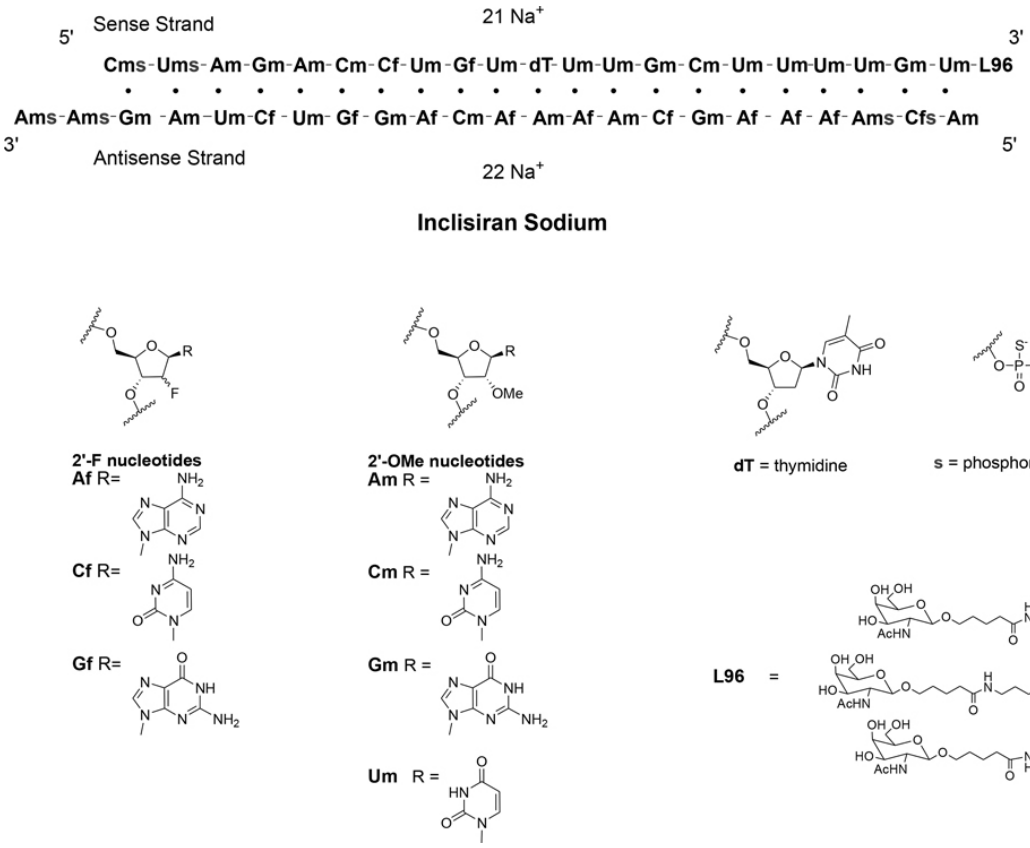
8.7 Hepatic Impairment

No dose adjustment is necessary in patients with mild to moderate hepatic impairment. LEQVIO has not been studied in patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

LEQVIO contains inclisiran sodium, a small interfering RNA (siRNA) directed to proprotein convertase subtilisin kexin type 9 (PCSK9) mRNA. Inclisiran contains a covalently linked ligand containing three N-acetylgalactosamine (GalNAc) residues to facilitate delivery to hepatocytes. With one exception, the 2'ribose moieties of the inclisiran sodium are present as 2'-F or 2'-OMe ribonucleotide. In addition, six of the terminal phosphodiester backbones are present as phosphorothioate linkages as indicated below.

The molecular formula of inclisiran sodium is $C_{529}H_{664}F_{12}N_{176}Na_{43}O_{316}P_{43}S_6$ and its molecular weight is 17,284.72 g/mol. It has the following structural formula:



Abbreviations: Af = adenine 2'-F ribonucleotide; Cf = cytosine 2'-F ribonucleotide; Gf = guanine 2'-F ribonucleotide; Am = adenine 2'-OMe ribonucleotide; Cm = cytosine 2'-OMe ribonucleotide; Gm = guanine 2'-OMe ribonucleotide; Um = uracil 2'-OMe ribonucleotide; L96 = triantennary GalNAc (N-acetyl-galactosamine)

LEQVIO is a sterile, preservative-free, clear, and colorless to pale yellow solution for subcutaneous use in a prefilled syringe. Each syringe contains 1.5 mL of solution containing the equivalent of 284 mg inclisiran (present as 300 mg inclisiran sodium salt). LEQVIO is formulated in Water for Injection and may also contain sodium hydroxide and/or phosphoric acid for pH adjustment to a target pH of 7.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Inclisiran is a double-stranded small interfering ribonucleic acid (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 mRNA for PCSK9. 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.

12.2 Pharmacodynamics

Following a single subcutaneous administration of 284 mg of inclisiran, LDL-C reduction was apparent within 14 days post dose. Mean reductions of 38% to 51% for LDL-C were observed 30 to 180 days post dose. At Day 180, LDL-C levels were still reduced by approximately 53%.

Following a dose at Day 1 and Day 90 of 284 mg of inclisiran, mean serum PCSK9 levels were reduced by approximately 75% and 69% at Day 120, and Day 180, respectively.

In the clinical studies, following four doses of LEQVIO at Day 1, Day 90 (3 months), Day 270 (~6 months) and Day 450 (~12 months), LDL-C, total cholesterol, ApoB, and non-HDL-C were reduced *[see Clinical Studies (14)]*.

Cardiac Electrophysiology

At a dose 3 times the maximum recommended dose, inclisiran does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Absorption

Following a single subcutaneous administration, systemic exposure to inclisiran increased in a linear and dose proportional manner over a range from 25 mg to 800 mg of inclisiran sodium. At the recommended dosing regimen of 284 mg of LEQVIO, plasma concentrations reached peak in approximately 4 hours post dose with a mean C_{max} of 509 ng/mL. Concentrations reached undetectable levels after 24 to 48 hours post dosing. The mean area under the plasma concentration-time curve from dosing extrapolated to infinity was 7,980 ng*h/mL. Pharmacokinetic findings following multiple subcutaneous administrations of LEQVIO were similar to single-dose administration.

Distribution

Inclisiran is 87% protein bound *in vitro* at the relevant clinical plasma concentrations. Following a single subcutaneous 284 mg dose of LEQVIO to healthy adults, the apparent volume of distribution is approximately 500 L. Inclisiran has been shown to have high uptake into, and selectively for the liver, the target organ for cholesterol lowering.

Elimination

The terminal elimination half-life of LEQVIO is approximately 9 hours, and no accumulation occurs with multiple dosing. Approximately 16% of LEQVIO is cleared through the kidney.

Metabolism

Inclisiran is primarily metabolized by nucleases to shorter nucleotides of varying length. Inclisiran is not a substrate for CYP450 or transporters.

Specific Populations

Male and Female Patients and Racial or Ethnic Groups

A population pharmacodynamic analysis was conducted on data from 4,328 patients. Age, body weight, gender, race, and creatinine clearance were found not to significantly influence inclisiran pharmacokinetics.

Patients with Renal Impairment

Pharmacokinetic analysis of data from a dedicated renal impairment study reported increases in inclisiran C_{max} and AUC of approximately 2.3 to 3.3-fold and 1.6 to 2.3-fold, respectively, in patients with mild, moderate or severe renal impairment, relative to patients with normal renal function. Despite the higher plasma exposures, reductions in LDL-C were similar across all groups based on renal function.

Patients with Hepatic Impairment

Pharmacokinetic analysis of data from a dedicated hepatic impairment study reported increases in inclisiran C_{max} and AUC of approximately 1.1- to 2.1-fold and 1.3- to 2.0-fold, respectively, in patients with mild and moderate hepatic impairment, relative to patients with normal hepatic function. Despite the higher plasma inclisiran exposures, reductions in LDL-C were similar between the groups of patients administered inclisiran with normal hepatic function and mild hepatic impairment. In patients with moderate hepatic impairment,

baseline PCSK9 levels were lower and reductions in LDL-C were less than those observed in patients with normal hepatic function. LEQVIO has not been studied in patients with severe hepatic impairment.

Drug Interaction Studies

No formal clinical drug interaction studies have been performed. The components of LEQVIO are not substrates, inhibitors or inducers of cytochrome P450 enzymes or transporters. In a population pharmacokinetic analysis, concomitant use of inclisiran did not have a clinically significant impact on atorvastatin or rosuvastatin concentrations. LEQVIO is not expected to cause drug-drug interactions or to be affected by inhibitors or inducers of cytochrome P450 enzymes or transporters.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of inclisiran.

The immunogenicity of LEQVIO has been evaluated using screening and confirmatory immunoassays for the detection of binding anti-inclisiran antibodies.

Samples from 1,830 patients in the placebo-controlled clinical trials were tested for anti-drug antibodies *[see Clinical Studies (14)]*. Confirmed positivity was detected in 33 (2%) patients prior to receiving LEQVIO and in 90 (5%) patients during the 18 months of treatment with LEQVIO. Approximately 31 (2%) LEQVIO-treated patients with a negative sample at baseline had a persistent anti-inclisiran antibody response, defined as two confirmed positive samples separated by at least 16 weeks or a single confirmed positive final sample. There was no identified clinically significant effect of anti-inclisiran antibodies on pharmacodynamics, safety, or effectiveness of LEQVIO over the treatment duration of 18 months. However, the long-term consequences of continuing LEQVIO treatment in the presence of anti-inclisiran binding antibodies are unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study, Sprague-Dawley rats were administered subcutaneous doses of 40, 95, or 250 mg/kg inclisiran once every 28 days (1, 3, or 8 times the MRHD, based on BSA comparison/dose). Inclisiran was not carcinogenic up to the highest dose tested.

In a 26-week study in RasH2Tg mice, subcutaneous doses of 300, 600, or 1,500 mg/kg once every 28 days were administered. Inclisiran was not carcinogenic up to the highest dose tested.

Inclisiran was not mutagenic or clastogenic in a standard battery of genotoxicity tests, including a bacterial mutagenicity assay, an *in vitro* chromosome aberration assay using human peripheral lymphocytes, and an *in vivo* bone marrow micronucleus assay in rats.

Fertility and early embryonic-development studies were conducted in male and female rats. In male rats, inclisiran was administered subcutaneously at dose levels of 10, 50, and 250 mg/kg every 2 weeks for 4 weeks before cohabitation through mating, and until termination between Days 64 and 67. In female rats, inclisiran was administered subcutaneously at dose levels of 10, 50, and 250 mg/kg once every 4 days beginning 14 days prior to cohabitation and through mating, followed by 10, 50, or 150 mg/kg once daily during the gestation period up to Gestation Day 7. There were no adverse effects on fertility up to the highest dose examined, corresponding to 8 times the MRHD, based on BSA comparison/dose.

14 CLINICAL STUDIES

The efficacy of LEQVIO 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. 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 1,561 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 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 or African American, 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 2 and Figure 1.

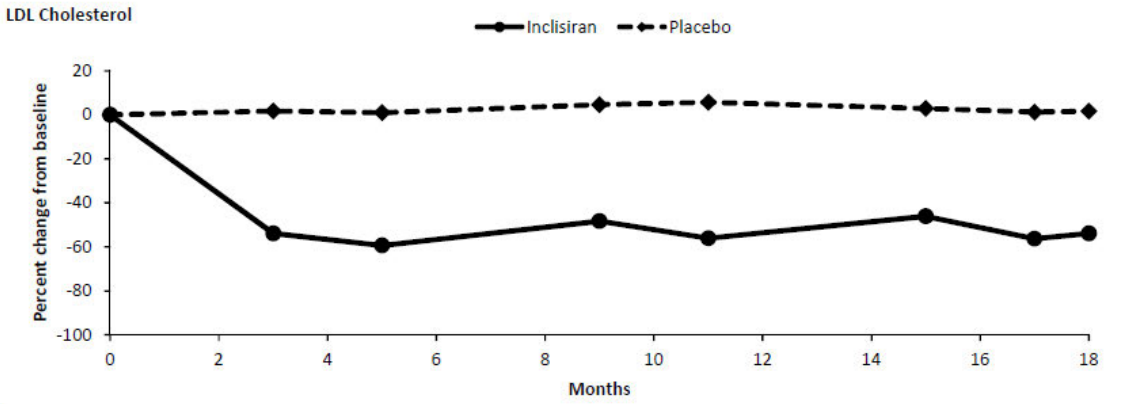
Table 2: Changes in Lipid Parameters in Patients with Hyperlipidemia and ASCVD on Maximally Tolerated Statin Therapy (Mean % Change from Baseline to Day 510 in Study 1)

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)

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 Hyperlipidemia and 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, and <1% were Asian; <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 3 and Figure 2.

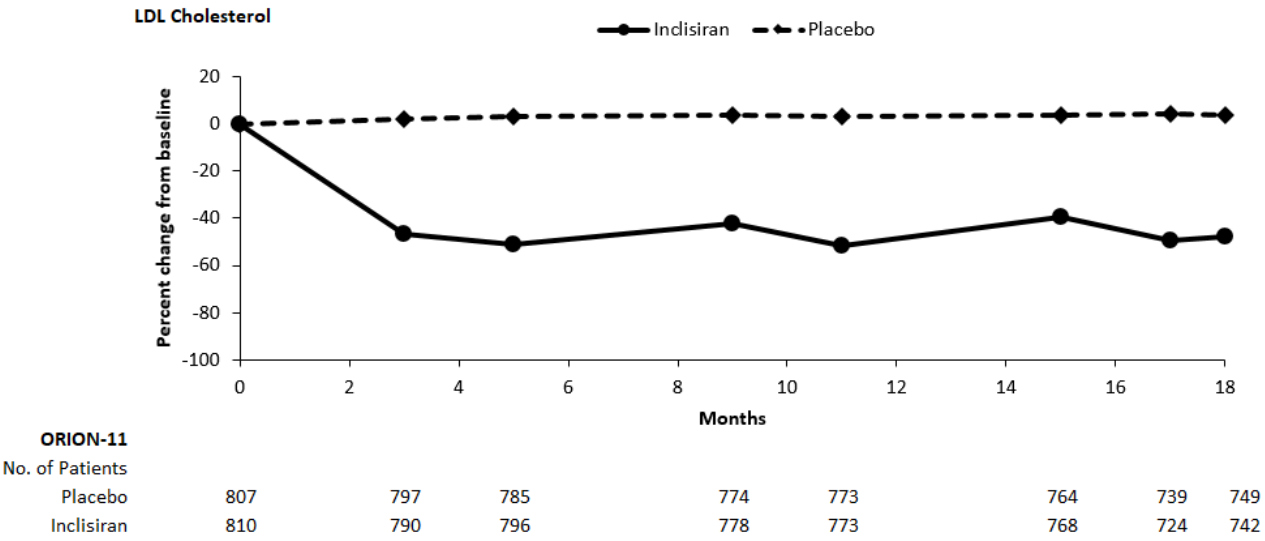
Table 3: Changes in Lipid Parameters in Patients with Hyperlipidemia and ASCVD or Increased Risk for ASCVD on Maximally Tolerated Statin Therapy (Mean % Change from Baseline to Day 510 in Study 2)

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)

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 Hyperlipidemia and ASCVD or Increased Risk for ASCVD on Maximally Tolerated Statin Therapy (Study 2)



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.

LDL-C Reduction in Patients with 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, and 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 4 and Figure 3.

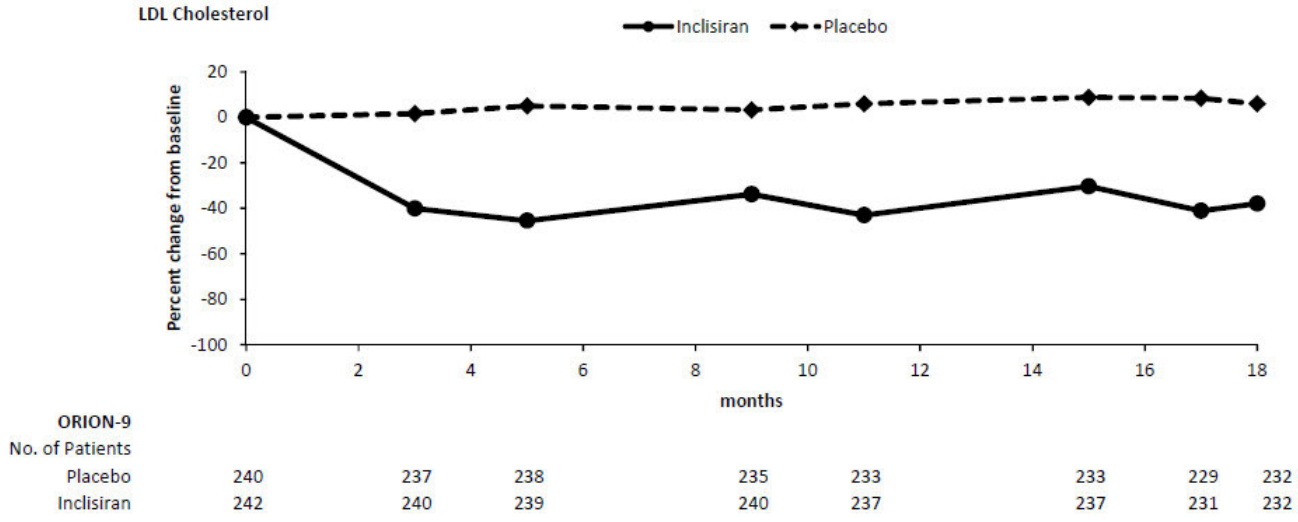
Table 4: Changes in Lipid Parameters in Patients with HeFH on Maximally Tolerated Statin Therapy (Mean % Change from Baseline to Day 510 in Study 3)

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)

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)



16 HOW SUPPLIED/STORAGE AND HANDLING

LEQVIO injection is a clear, colorless to pale yellow solution, 284 mg/1.5 mL (189 mg/mL) of inclisiran supplied as:

Carton containing 1 single-dose prefilled syringe:

NDC 0078-1000-60

Store LEQVIO 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) [see USP, Controlled Room Temperature (CRT)].

17 PATIENT COUNSELING INFORMATION

Pregnancy

Advise pregnant patients and patients who can become pregnant of the potential risk to a fetus. Advise patients to inform their healthcare provider of a known or suspected pregnancy to discuss if LEQVIO should be discontinued *[see Use in Specific Populations (8.1)]*.

Injection Site Reactions

Advise patients that injection site reactions can occur with LEQVIO *[see Adverse Reactions (6.1)]*.

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

For more information, visit www.leqvio.com or call 1-833-LEQVIO2 (1-833-537-8462).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214012Orig1s009

CLINICAL REVIEW(S)

Division of Diabetes, Lipids, and Obesity
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

PRIOR APPROVAL SUPPLEMENT AND CLINICAL LABELING REVIEW

Application: NDA 214012, Supplement 009
EDR sequence number: 0117
Name of Drug: Inclisiran/ Leqvio
Indication: LDL-C lowering
Applicant: Novartis Pharmaceutical Corporation
Date Received: 05/25/2023
Date Review Completed: 6/28/2023

Executive Summary

Novartis Pharmaceuticals Corporation under NDA 214012, Supplement 009, submitted a Prior Approval Supplement (PAS) in response to an FDA request to submit a revised label for Leqvio (inclisiran) for NDA 214012. In a letter dated May 5, 2023, the Agency issued a supplement request letter to update the Prescribing Information (PI) for Leqvio (inclisiran) injection. Based on the Agency's review of the currently approved PI and given the positive cardiovascular outcomes trials in the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor class as well as the safety and effectiveness data for inclisiran, the Agency simplified the indication language and removed the limitations of use statement. Additionally, the Agency updated other sections of the PI to conform to current and draft labeling guidances (see the Prescribing Information section below).

The Applicant (Novartis) accepted all changes proposed by FDA in the PI except for minor word clarifications and a slight change in the FDA proposed values in the Clinical Trials section of the PI for Study 2 (ORION-11). These minor value corrections were confirmed by the FDA review team. Additionally, as requested by FDA for Study 2 (ORION-11), the data from the subjects with atherosclerotic cardiovascular disease (ASCVD) risk equivalent was added to this section. The Applicant confirmed the FDA's edits defining the full population of subjects (patients with ASCVD and patients without ASCVD but at increased risk of ASCVD) that participated in this trial.

On June 22, 2023, FDA sent the Applicant a revised PI with minor changes to the Applicant's proposed PI (such as (b) (4) and moving ethnicity information to the end of the sentence in Section 6.1). The Applicant agreed to these minor changes.

The Office of Prescription Drug Promotion (OPDP) reviewed the proposed PI for supplement 9 for Leqvio and did not have any comments (refer to the review by Ankur Kalola, Regulatory Review Officer, OPDP, in DARRTS dated June 20, 2023).

NDA 214012/S-009 should be approved with the agreed upon Prescribing Information.

Background

Leqvio (inclisiran) is a small interfering ribonucleic acid (siRNA) that targets proprotein convertase subtilisin/kexin type 9 (PCSK9). NDA 214012 for Leqvio was approved on December 22, 2021, indicated 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).

Leqvio is currently supplied as a single-dose PFS for administration by a healthcare professional.

Prescribing Information

The last FDA approved PI is dated December 22, 2021.

Given the cardiovascular risk reduction seen with other PCSK9 inhibitors, the Agency has simplified the indication language and removed the limitation of use statement. Additionally, FDA updated other sections to conform to recent labeling guidances. A summary table of significant changes made to the Full Prescribing Information (PI) is below. Highlights and Table of Contents were revised for consistency with the rest of the PI. Additionally, there were minor formatting changes and editing for clarity.

Prior Approval Supplement

Labeling Review

Major Prescribing Information Changes

Section	Major changes
[1] Indications and Use	▪ Given the positive cardiovascular outcomes trials in the PCK9 inhibitor class and safety and effectiveness data for inclisiran: o Simplified the indication to remove “maximally tolerated” statin and focus on lowering low-density lipoprotein cholesterol (LDL-C) in primary hyperlipidemia rather than atherosclerotic cardiovascular disease (ASCVD)

	o Removed the limitations of use for cardiovascular morbidity and mortality
[2] Dosage and Administration	▪ Revised concomitant therapy to reflect “statin therapy” instead of “maximally tolerated” statin therapy to align with the revised indication.
[6] Adverse Reactions	▪ Added ethnicity data for safety population, rounded common adverse reactions to nearest integer to improve comprehension. ▪ Relocated immunogenicity data to Section 12.6 for consistency with the draft Immunogenicity labeling guidance (2022).
[8] Use in Specific Populations [8.5] Geriatric Use	▪ Updated language for consistency with the Geriatric labeling guidance (2020).
[12] Clinical Pharmacology [12.6] Immunogenicity	▪ Added immunogenicity guidance and updated language for consistency with the draft Immunogenicity labeling guidance (2022).
[14] Clinical studies	▪ Added data from patients with CVD risk equivalents from Study 2, for consistency with revised indication.

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/s/

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214012Orig1s009

OTHER REVIEW(S)

Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 214012/S-009 Prior Approval Labeling Supplement

Name of Drug: Leqvio (inclisiran) injection

Applicant: Novartis Pharmaceuticals Corporation

Labeling Reviewed

Submission Date: May 25, 2023

Receipt Date: May 25, 2023

Background and Summary Description:

(b) (4)

(b) (4) The Applicant submitted a PAS (S-009, the subject of this review) on May 25, 2023, to address the requested labeling changes in the May 5, 2023, letter.

Review

The labeling was reviewed by the Office of Prescription Drug Promotion (OPDP)[1] and the Division of Diabetes, Lipid Disorders, and Obesity[2].

The proposed PI was compared to the currently approved version using the Microsoft Word compare feature. Refer to the attached document for a complete list of changes.

1 Kalola, A. OPDP Memorandum. DARRTS Reference ID: 5193663. June 20, 2023.
2 Craig, E. Prior Approval Supplement and Clinical Labeling Review. DARRTS Reference ID: 5199135. June 28, 2023.

Labeling Piece	Currently Approved Labeling and Date	Final Labeling Submission Date
Prescribing Information	NDA 214012 ORIG-1 December 22, 2021	NDA 214012/S-009 June 23, 2023

Recommendations

An approval letter should be issued for NDA 214012/S-009

Ron Picking	June 27, 2023
Regulatory Project Manager	Date
Elizabeth Solomon	June 28, 2023
Chief, Project Management Staff	Date

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RONALD D PICKING
06/29/2023 10:14:36 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 20, 2023

To: Ron Picking, Regulatory Project Manager, Division of Diabetes, Lipid Disorders and Obesity

Melinda Wilson, Associate Director for Labeling, DDLO

From: Ankur Kalola, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, Team Leader, OPDP

Subject: OPDP Labeling Comments for LEQVIO® (inclisiran) injection, for subcutaneous use

NDA: 214012, S-09

Background:

In response to DDLO's consult request dated May 30, 2023, OPDP has reviewed the proposed Prescribing Information (PI) for supplement 9 for Leqvio. This supplement provides for changes to the indication section of the PI and other updates to conform to recent labeling guidances.

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on June 13, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Ankur Kalola at 301-856-4562 or Ankur.Kalola@fda.hhs.gov.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214012Orig1s009

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

From: PickingIII, Ronald
Sent: Thu, 22 Jun 2023 22:00:15 +0000
To: Fassihi, Mona
Cc: Toma, Steven
Subject: NDA 214012/S-009 Leqvio, PI
Attachments: NDA 214012 S-009 PI to Novartis 6.22.23.docx

Hi Mona,

Please see the attached labeling with our comments for NDA 214012/S-009.

Please accept all edits with which you agree. The document that you return to us should only show in tracked changes: (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. If you do not agree with an FDA edit, add a comment bubble, that begins with "Applicant response to FDA change" or "Applicant comment."

We ask that you provide the revised labeling by **Thursday June 29, 2023**. The labeling can be sent to me via email and does not need to be submitted to the application until we have agreed-upon labeling.

We remind you that these edits do not reflect the final regulatory decision for this application.

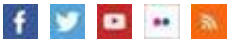
Please confirm receipt.

Thanks,

Ron

Ron Picking, PharmD
Regulatory Project Manager

Diabetes, Lipid Disorders, and Obesity
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-402-3211
Fax: 301.595.2123
Ronald.PickingIII@fda.hhs.gov



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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-OPDP-RPM	Ron Picking RPM OCHEN/DDLO 240-402-3211

REQUEST DATE:	IND NO.	NDA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
5/30/2023		214012/S-009	

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Leqvio (inclisiran)	Standard	PCSK9 siRNA	

NAME OF FIRM:	
Novartis	PDUFA Date: November 25, 2023

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☒ PRESCRIBING INFORMATION (PI)
☐ PATIENT PACKAGE INSERT (PPI)
☐ CARTON/CONTAINER LABELING
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☐ IND
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☒ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☒ LABELING REVISION

For OSE USE ONLY
☐ REMS

EDR link to submission: EDR Location: \\CDSESUB1\evsprod\NDA214012\0117

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS: This is a labeling supplement in response to our May 5, 2023 supplement request letter. At this time no internal meetings are planned. We will send labeling when it is substantially complete.

Review Team
Clinical: Iffat Chowdhury/Eileen Craig
ADL: Melinda Wilson

SIGNATURE OF REQUESTER Ron Picking

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) X eMAIL ☐ HAND

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NDA 214012/S-009

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Novartis Pharmaceuticals Corporation
Attention: Mona Fassihi, PharmD, MS
Senior Global Program Regulatory Manager, Regulatory Affairs
One Health Plaza, Building 337
East Hanover, NJ 07936-1080

Dear Dr. Fassihi:

We have received your supplemental new drug application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 214012

SUPPLEMENT NUMBER: S-009

PRODUCT NAME: Leqvio (inclisiran) injection

DATE OF SUBMISSION: May 25, 2023

DATE OF RECEIPT: May 25, 2023

This supplemental application proposes changes to the Leqvio Prescribing Information that were requested in our May 5, 2023, Prior Approval Supplement Request letter, and other minor changes.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 24, 2023, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be November 25, 2023.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[1] Failure to submit the content of labeling in SPL format may result in a refusal-to-file action.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

If you have questions, call me at 240-402-3211.

Sincerely,

{See appended electronic signature page}

Ron Picking, Pharm.D.
Regulatory Project Manager
Diabetes, Lipid Disorders, and Obesity
Division of Regulatory Operations for Cardiology,
Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

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