

NDA 214012

**NDA APPROVAL**

Novartis Pharmaceuticals Corporation  
Attention: Mona Fassihi, PharmD  
Global Program Regulatory Manager, Regulatory Affairs  
One Health Plaza, Building 315  
East Hanover, NJ 07936-1080

Dear Dr. Fassihi:

Please refer to your new drug application (NDA) dated and received December 23, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Leqvio (inclisiran) injection.

We acknowledge receipt of your amendment dated July 1, 2021, which constituted a complete response to our December 18, 2020, action letter.

This NDA provides for the use of Leqvio (inclisiran) injection 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).

### **APPROVAL & LABELING**

We have completed our review of this application, as amended. 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.

- Revision date updated in the Highlights of Prescribing Information to reflect NDA 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.<sup>1</sup> Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information) as well as annual reportable changes not included in the

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<sup>1</sup> <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

enclosed labeling. 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*.<sup>2</sup>

The SPL will be accessible via publicly available labeling repositories.

### **CARTON AND CONTAINER LABELING**

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling and carton and container labeling submitted on November 29, 2021, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 214012.**” Approval of this submission by FDA is not required before the labeling is used.

### **DATING PERIOD**

Based on the stability data submitted to date, the expiry dating period for Leqvio (inclisiran) injection shall be 24 months from the date of manufacture when stored at 25 °C in the proposed commercial packaging.

### **ADVISORY COMMITTEE**

Your application for Leqvio was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease and because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

### **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.

We are waiving the pediatric study requirement for pediatric patients with non-familial hypercholesterolemia with clinical atherosclerotic cardiovascular disease and elevated

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<sup>2</sup> 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>.

LDL-C for this application because necessary studies are impossible or highly impracticable as this condition rarely occurs in pediatric patients.

We are waiving the pediatric study requirement for ages birth to <8 years of age (or <6 years of age and on apheresis) for elevated LDL-C with HeFH because necessary studies are impossible or highly impracticable. This is because the patient population appropriate for pharmacologic intervention is exceedingly small.

We are deferring submission of your pediatric studies for ages 8 to <18 years for elevated LDL-C with HeFH for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. These required studies are listed below.

- 4186-1 Conduct a two-part (double-blind inclisiran versus placebo [Year 1] followed by open-label with placebo-treated subjects switched to inclisiran [Year 2]), multicenter study to evaluate safety, tolerability, and efficacy of inclisiran in children (aged 12 to <18 years) with heterozygous familial hypercholesterolemia (HeFH).

Study Completion: June 2025  
Final Report Submission: December 2025

- 4186-2 Conduct a two-part (double-blind inclisiran versus placebo [Year 1] followed by open-label with placebo-treated subjects switched to inclisiran [Year 2]), multicenter study to evaluate safety, tolerability, and efficacy of inclisiran in children [aged 6-7 (if on plasma apheresis) or 8 to <12 years] with heterozygous familial hypercholesterolemia (HeFH).

Draft Protocol Submission: December 2023  
Final Protocol Submission: June 2024  
Study Completion: June 2027  
Final Report Submission: December 2027

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.<sup>3</sup>

Submit the protocols to your IND 127589, with a cross-reference letter to this NDA.

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<sup>3</sup> See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019)*.

<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

Reports of these required pediatric postmarketing studies must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of pregnancy complications and adverse effects on the developing fetus and neonate.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

- 4186-3 Conduct a worldwide, descriptive study that collects prospective and retrospective data in women exposed to Leqvio during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.

The timetable you submitted on December 6, 2021, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	March 2022
Interim Report Submission:	March 2022
	March 2023
	March 2024
	March 2025
	March 2026
	March 2027
	March 2028
	March 2029
	March 2030
Study Completion:	December 2030
Final Report Submission:	July 2031

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.<sup>4</sup>

Submit clinical protocol(s) to your IND 127589 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

### **POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitments:

- 4186-4 Validate the sensitivity and all other validation parameters except cutpoints for the ELISA method used to detect anti-inclisiran-reactive IgG/IgM antibodies in human serum, employing an affinity-purified anti-inclisiran antibody positive control (i.e., Rabbit AntiKLH-TTRSC-2017 antiserum) to ensure that the assay is sensitive, specific, and selective for

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<sup>4</sup> See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019)*.  
<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

measurement of ADA responses. Validate the assay in accordance with the FDA Guidance for Industry entitled “Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection”.

The timetable you submitted on December 6, 2021, states that you will conduct this study according to the following schedule:

Study Completion: August 2022  
Final Report Submission: October 2022

- 4186-5 Re-evaluate anti-inclisiran-reactive IgG/IgM antibodies in all clinical samples using the appropriately validated assay. Re-assess the impact of anti-inclisiran-reactive IgG/IgM antibodies on pharmacokinetics, efficacy, and safety.

The timetable you submitted on December 6, 2021, states that you will conduct this study according to the following schedule:

Study Completion: July 2023  
Final Report Submission: August 2023

**POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitments:

- 4186-6 Reevaluate and tighten the purity and impurity content specification for finished product, based on additional batch release and stability data to be available from commercial scale Sandoz GmbH drug product batches, manufactured using (b) (4)

The timetable you submitted on November 23, 2021, states that you will conduct this study according to the following schedule:

Final Report Submission: November 2023

- 4186-7 Evaluate and provide the end of shelf-life leachable study data for stability batches manufactured at Sandoz GmbH.

The timetable you submitted on November 23, 2021, states that you will conduct this study according to the following schedule:

Final Report Submission: January 2024

## **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*.<sup>5</sup>

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.<sup>6</sup> Information and Instructions for completing the form can be found at FDA.gov.<sup>7</sup>

## **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.<sup>8</sup>

## **POST APPROVAL FEEDBACK MEETING**

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

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<sup>5</sup> For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

<sup>6</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

<sup>7</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

<sup>8</sup> <https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products>

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

Sincerely,

*{See appended electronic signature page}*

Lisa B. Yanoff, M.D.  
Deputy Director  
Office of Cardiology, Hematology,  
Endocrinology, and Nephrology  
Office of New Drugs  
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
- Carton and Container Labeling

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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.**  
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