NDA 214012/S-017
NDA 214012/S-018

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT

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

Dear Dr. Fassihi:

Please refer to your supplemental new drug applications (sNDAs) and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Leqvio (inclisiran) injection.

Supplement 017

This Prior Approval sNDA, dated and received August 12, 2025, provides for the following labeling changes:

> Modifications to the Prescribing Information to add results of pediatric study ORION-16 (CKJX839C12301), titled, *Two part (double-blind inclisiran versus placebo [Year 1] followed by open-label inclisiran [Year 2]) randomized multicenter study to evaluate safety, tolerability, and efficacy of inclisiran in adolescents (12 to less than 18 years) with heterozygous familial hypercholesterolemia and elevated LDL-cholesterol*, and expand the currently approved indication to include pediatric patients 12 years and older with heterozygous familial hypercholesterolemia (HeFH).

This study was conducted to partially fulfill the Written Request issued November 1, 2019, and amended on October 20, 2022, and to address the following postmarketing requirement (PMR) established in the December 22, 2021, NDA Approval letter:

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).

Supplement 018

This Prior Approval sNDA, dated and received August 13, 2025, provides for the following labeling changes:

> Modifications to the Prescribing Information to add results of pediatric study ORION-13 (CKJX839C12302), titled, *Two part (double-blind inclisiran versus placebo [Year 1] followed by open-label inclisiran [Year 2]) randomized multicenter study to evaluate safety, tolerability, and efficacy of inclisiran in adolescents (12 to less than 18 years) with homozygous familial hypercholesterolemia and elevated LDL-cholesterol*, and add a new indication for pediatric patients 12 years and older with homozygous familial hypercholesterolemia (HoFH).

This study was conducted to partially fulfill the Written Request issued November 1, 2019, and amended on October 20, 2022.

These supplements also provide for the following Prescribing Information changes:

1. Addition of 'anaphylaxis' to Sections 4, *Contraindications*, and 6.2, *Postmarketing Experience*

2. Addition of 'hypersensitivity reactions' to Section 5, *Warnings and Precautions*

3. Addition of 'pruritus' to Section 6.2, *Postmarketing Experience*

4. Additional edits made throughout the Prescribing Information to modernize with current labeling guidances, clarify language, and improve readability and organization of information

APPROVAL & LABELING

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Supplement 17 provides for pediatric information pursuant to both the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Act (PREA). Supplement 18 provides for pediatric labeling text pursuant to the BPCA.

This approval is in response to both a written request and PREA PMR.

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 and Instructions for Use), 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.

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.

We note that you have fulfilled the pediatric study requirement for ages 12 years to <18 years for elevated LDL-C with HeFH.

Because this drug product for elevated LDL-C with HoFH has an orphan drug designation, you are exempt from this requirement for that patient population.

FULFILLMENT OF POSTMARKETING REQUIREMENT

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

Your submission dated August 12, 2025, contains the final report for PMR 4186-1, cited above.

We have reviewed your submission and conclude that the above requirement was fulfilled.

We remind you that there are postmarketing requirements listed in the December 22, 2021, approval letter that are still open.

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]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety- related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

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

[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

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, contact Christine Wright, Regulatory Project Manager, at Anne.Wright@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

John Sharretts, MD
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

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Instructions for Use (version approved June 6, 2024)

[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
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