NDA 213051/S-020
NDA 213051/S-021

SUPPLEMENT APPROVAL

Novo Nordisk Inc.
Attention: Jigisha Varia
Director, Regulatory Affairs
P.O Box 846
800 Scudders Mill Road
Plainsboro, NJ 08536

Dear Jigisha Varia:

Please refer to your supplemental new drug applications (sNDAs) dated and received February 9 and June 6, 2024, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Rybelsus (semaglutide) tablets.

These Prior Approval sNDAs provide for the following:

S-020: Addition of Rybelsus formulation R2, new recommended dosage for formulation R2, and recommendations for switching between formulation R1 and R2. S-020 also provides for addition of a new drug product manufacturing site, Novo Nordisk Pharmaceutical Industries, Durham, North Carolina, (FEI: 3016799712) with a change in the drug product manufacturing process to use (b) (4) manufacturing process.

S-021: Revisions to subsection 8.2 *Lactation* of the Prescribing Information (PI) to include relevant results of trial NN9924-4669, entitled, *A trial investigating semaglutide and SNAC concentrations in breastmilk following administration of multiple doses of oral semaglutide in healthy, lactating females*.

This trial was conducted to address the following postmarketing requirement (PMR) established in the September 20, 2019, Approval letter.

3692-3 Conduct a milk-only lactation study in lactating women who have received Rybelsus (semaglutide) tablets therapeutically to assess concentrations of semaglutide and salcaprozate sodium (SNAC) in breast milk using a validated assay

During review of these supplements, editorial revisions were made to subsection 5.2 *Acute Pancreatitis* of the PI to improve clarity, “Severe Gastrointestinal Adverse Reactions” warning was added to section 5.6 WARNINGS AND PRECAUTIONS of the PI to align with the labeling for other glucagon-like peptide-1 (GLP-1) receptor agonists,

and “dysesthesia” and “alopecia” were added to subsection 6.1 *Clinical Trials Experience* of the PI.

The Medication Guide was also revised to reflect corresponding changes in the PI.

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.

- Margin marks added to the PI to reflect Recent Major Changes
- Formatting of the Recent Major Changes section in the Highlights of the PI

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

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 Medication Guide), 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

[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.

Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, 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 213051/S-020**." Approval of this submission by FDA is not required before the labeling is used.

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.

The following information was originally conveyed in the approval letter for NDA 213051, dated September 20, 2019, and is relied upon to satisfy the requirements of PREA for S-020. A new PMR set number was assigned for administrative purposes.

We are waiving the pediatric study requirement for ages 0 through 9 years (inclusive) because necessary studies are impossible or highly impracticable. This is because there are too few children in this age range with type 2 diabetes mellitus to study.

We are deferring submission of your pediatric study for ages 10 to 17 years (inclusive) for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required under section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the FDCA. This required study is listed below.

4766-1 Conduct a 52-week, randomized, double-blind, placebo-controlled parallel group study of the safety and efficacy of Rybelsus (semaglutide) tablets for the treatment of type 2 diabetes mellitus in pediatric patients ages 10

to 17 years (inclusive). Background therapy will consist of either metformin, insulin, or metformin plus insulin.

Draft Protocol Submission: November 2019
Final Protocol Submission: May 2020
Study Completion: December 2026
Final Report Submission: June 2027

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).

If you have any questions, contact Lindsey Kelly, Regulatory Project Manager, at 301-837-7654 or Lindsey.Kelly@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Patrick Archdeacon, M.D.
Deputy 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
  - Medication Guide
- Carton and Container Labeling

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/

PATRICK ARCHDEACON
12/09/2024 03:25:43 PM