

NDA 213051/S-024  
NDA 213051/S-028  
NDA 213051/S-029

## 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 December 18, 2024, March 21, and June 20, 2025, respectively, 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:

S-024:

- Addition of the new indication, “to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in adults with type 2 diabetes mellitus who are at high risk for these events,” in Section 1 *Indications and Usage* of the Rybelsus Prescribing Information (PI) and addition of associated data on safety and effectiveness in subsections 5.8, 6.1, and 14.4 of the PI.
- Removal of the Limitation of Use for treatment of type 1 diabetes mellitus in Section 1 of the PI
- Updates to the Medication Guide (MG) for alignment with the PI.

S-028:

- Revisions to the Warnings and Precautions Section 5.2 Acute Pancreatitis and 5.5 Acute Kidney Injury Due to Volume Depletion for consistency with the class. Section 17 was updated to reflect these changes.
- Revisions to Warnings and Precautions Section 5.6 Severe Gastrointestinal Adverse Reactions to include the statement “Severe gastrointestinal adverse

reactions have also been reported postmarketing with glucagon-like peptide (GLP)-1 receptor agonists.”

- Revisions to the PI to add ‘intestinal obstruction, severe constipation including fecal impaction’ and ‘acute kidney injury’ in Section 6.2, Postmarketing Experience.

S-029: Revisions to the PI to add ‘headache’ in Section 6.2, Postmarketing Experience.

## **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.

## **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](http://FDA.gov).<sup>1</sup> Content of labeling must be identical to the enclosed labeling (text for the PI and MG), 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*.<sup>2</sup>

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).

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

<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>.

## **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 this supplemental application because necessary studies are impossible or highly impracticable as established cardiovascular disease is an adult-related condition.

## **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>3</sup>

You must submit final promotional materials and PI, 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.<sup>4</sup> Information and Instructions for completing the form can be found at FDA.gov.<sup>5</sup>

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

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<sup>3</sup> For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

<sup>4</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

<sup>5</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

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).

If you have any questions, contact Lindsey Kelly, Regulatory Project Manager at [Lindsey.Kelly@fda.hhs.gov](mailto:Lindsey.Kelly@fda.hhs.gov).

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

### ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

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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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/s/  
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JOHN M SHARRETTS  
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