NDA 217806/S-042

SUPPLEMENT APPROVAL

Eli Lilly and Company
Attention: Teresa Berg
Senior Director, Global Regulatory Affairs
Lily Corporate Center
Indianapolis, IN 46285

Dear Teresa Berg:

Please refer to your supplemental new drug application (sNDA) dated and received November 14, 2025, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zepbound (tirzepatide) injection, and Zepbound KwikPen (tirzepatide) injection.

We also refer to our Notification of Newly Identified Safety Signal (NISS) email dated April 28, 2025, in which we informed you that we are evaluating a NISS regarding intestinal obstruction and fecal impaction for the glucagon-like peptide-1 (GLP-1) receptor agonist class, of which Zepbound is a member. On October 14, 2025, we issued a supplement request letter (SRL) to update the labeling based on our evaluation of this safety signal.

This Prior Approval sNDA provides for the following changes in response to the October 14, 2025, SRL:

(1) Addition of the following statement in Section 5 Warnings and Precautions, under 'Severe Gastrointestinal Adverse Reactions': "Severe gastrointestinal adverse reactions have also been reported postmarketing with GLP-1 receptor agonists."

(2) Addition of the following in Section 6 Adverse Reactions, under 'Postmarketing Experience': "intestinal obstruction, severe constipation including fecal impaction"

We also refer to our NISS letter dated July 21, 2023, in which we informed you that we were evaluating a NISS for suicidal ideation for the glucagon-like peptide-1 receptor agonist (GLP-1 RA) class, of which Zepbound is a member. On January 13, 2026, we issued an SRL requesting the removal of information regarding suicidal ideation from the Zepbound label. As discussed, these changes were made during review of S-042 rather than in a separate supplement. As such, this supplement also provides for the following:

(1) Removal of subsection 5.9, Suicidal Ideation and Behavior, from the Warnings and Precautions section of the Prescribing Information (PI) and updates to the Highlights of PI, Table of Contents, Section 6, Section 17, and the Recent Major Changes section accordingly.

(2) Removal of 'depression or thoughts of suicide' from the possible side effects section in the Medication Guide (MG).

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.[1] Content of labeling must be identical to the enclosed labeling (text for the PI, Instructions for Use, 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*.[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).

[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.

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 supplemental 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]

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

[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

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, contact Marisa Petruccelli, Safety Regulatory Project Manager, at marisa.petruccelli@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Monika Houstoun, Pharm.D., M.P.H.
Deputy Director for Safety
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
  - Instructions for Use – KwikPen (version previously approved January 20, 2026)
  - Instructions for Use- multi-dose vial (version previously approved January 7, 2026)
  - Instructions for Use- single dose vial (version previously approved March 28, 2024)
  - Instructions for Use- single dose pen (version previously approved November 8, 2023)

[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/

MONIKA A HOUSTOUN
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