CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

217806Orig1s000

Trade Name:	Zepbound injection.
Generic or Proper Name:	tirzepatide
Sponsor:	Eli Lilly and Company
Approval Date:	November 8, 2023
Indication:	As an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of: • 30 kg/m2 or greater (obesity) or • 27 kg/m2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes mellitus, obstructive sleep apnea, or cardiovascular disease).

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 217806

NDA APPROVAL

Eli Lilly and Company
Attention: Ingrid Hensley, PhD
Senior Director, Global Regulatory Affairs- North America
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Dr. Hensley:

Please refer to your new drug application (NDA) dated and received May 8, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zepbound (tirzepatide) injection.

This NDA provides for the use of Zepbound (tirzepatide) injection as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:

- 30 kg/m^2 or greater (obesity) or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes mellitus, obstructive sleep apnea, or cardiovascular disease).

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.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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, Instructions for Use, and Medication Guide) 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 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, 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 *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 217806**." 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 Zepbound (tirzepatide) injection shall be 24 months from the date of manufacture when stored at 2°C to 8°C (36°F to 46°F).

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 studies requirement for ages 0 to 5 years inclusive, because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group **and** is not likely to be used in a substantial number of pediatric patients in this group. FDA proposes that studies of weight management products be conducted in children who are 7 years or older, while the European Medicines Agency (EMA) guideline on the clinical evaluation of medicinal products used in weight management in children recommends enrollment of children

[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.

aged 6 years and older in clinical trials. As the pediatric study plan is a global program, the EMA guideline will be applied.

We are deferring submission of your pediatric studies for ages 6 to 17 years (inclusive) 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.

4534-1 Conduct a 72-week, randomized, double-blind, placebo-controlled, multicenter, parallel-arm study to evaluate the safety and efficacy of Zepbound (tirzepatide) as an adjunct to lifestyle intervention for chronic weight management in pediatric patients aged 12 to 17 years (inclusive) with obesity.

Study Completion:	February 2027
Final Report Submission:	August 2027

4534-2 Conduct a safety, tolerability, pharmacokinetic, and pharmacodynamic study of Zepbound (tirzepatide) administered subcutaneously in pediatric patients aged 6 to 11 years (inclusive) with obesity. Data from this study should be considered when choosing dose(s) for the safety and efficacy trial in this pediatric population.

Study Completion:	May 2025
Final Report Submission:	October 2025

4534-3 Conduct a 72-week, randomized, double-blind, placebo-controlled, multicenter, parallel-arm study to evaluate the safety and efficacy of Zepbound (tirzepatide) as an adjunct to lifestyle intervention for chronic weight management in pediatric patients aged 6 to 11 years (inclusive) with obesity.

Draft Protocol Submission:	October 2025
Final Protocol Submission:	April 2026
Study Completion:	December 2029
Final Report Submission:	June 2030

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.[3]

Submit the protocols to your IND 139721, with a cross-reference letter to this NDA. 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 assess a signal of a serious risk of medullary thyroid carcinoma or to identify an unexpected serious risk of maternal and fetal adverse reactions.

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:

4534-4 Collect global data from a prospective pregnancy exposure registry, preferably a disease-based multi-product pregnancy registry, using a registry-based cohort study to compare the maternal, fetal, and infant outcomes of women exposed to Zepbound (tirzepatide) for chronic weight management during pregnancy with unexposed comparator population(s). Align the study protocol with protocol(s) outside the United States to reach the target sample size. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal

[3] 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.

growth and development, will be assessed through at least the first year of life.

The timetable you submitted on November 6, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	June 2024
Final Protocol Submission:	June 2025
Interim Report Submission:	June 2026
	June 2028
	June 2030
	June 2032
	June 2034
Study Completion:	June 2035
Final Report Submission:	June 2036

4534-5 Conduct an additional pregnancy study that uses a different design from the pregnancy exposure registry (for example a cohort study using claims or electronic medical record data) to compare the risks and prevalence of pregnancy and infant outcomes (including but not limited to major congenital malformations, spontaneous abortions, stillbirths, small-for-gestational-age births, preterm births, and postnatal growth and development) between women exposed to Zepbound (tirzepatide) for chronic weight management during pregnancy and unexposed comparator population(s).

The timetable you submitted on November 6, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	September 2024
Final Protocol Submission:	September 2025
Interim Report Submission:	September 2026
	September 2028
	September 2030
Study Completion:	September 2031
Final Report Submission:	September 2032

4534-6 Conduct a medullary thyroid carcinoma registry-based case series of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of Zepbound (tirzepatide) for the treatment of overweight and obesity into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to the use of Zepbound (tirzepatide) for the treatment of obesity/overweight.

The timetable you submitted on November 1, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	May 2024
Final Protocol Submission:	May 2025
Interim Report Submission:	May 2026
	May 2027
	May 2028
	May 2029
	May 2030
	May 2031
	May 2032
	May 2033
	May 2034
	May 2035
	May 2036
	May 2037
	May 2038
	May 2039
	May 2040
Study Completion:	August 2040
Final Report Submission:	August 2041

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.[4]

Submit clinical protocol(s) to your IND 139721 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

[4] 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.

undertaken to investigate a safety issue. Section 506B(a)(1) 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(a)(1) 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.

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.*[5]

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.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

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.[8]

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[8] https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products

strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website[9].

If you have any questions, call Arati B. Kamath, Ph.D., Regulatory Project Manager, at (301) 796-3159.

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
  - Instructions for Use
- Carton and Container Labeling

[9] https://www.uspnf.com/

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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