

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**217806Orig1s000**

**NON-CLINICAL REVIEW(S)**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION**

Application number: 217806  
Supporting document/s: 1  
Applicant's letter date: November 17, 2022  
CDER stamp date: November 17, 2022  
Product: Zepbound (tirzepatide)  
Indication: Adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults  
Applicant: Eli Lilly and Co  
Review Division: Division of Diabetes, Lipid Disorders, and Obesity  
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# 1 Executive Summary

## 1.1 Introduction

Zepbound (tirzepatide) was developed by Eli Lilly and Co as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults.

## 1.2 Brief Discussion of Nonclinical Findings

Tirzepatide is a 39 amino acid peptide agonist of the glucose-dependent insulinotropic polypeptide receptor (GIPR) and glucagon-like peptide 1 receptor (GLP-1R). No new toxicology studies were conducted to support the weight management indication, as a complete nonclinical program was conducted and reviewed to support the diabetic indication (IND 128801 and NDA 215866). No new nonclinical studies were required as the dosage of tirzepatide (up to 15 mg once weekly) and the age group (adults) are identical to those in the approved indication. Refer to nonclinical reviews under IND 128801 (DARRTS, 10/13/2022) and NDA 215866 (DARRTS, 03/16/2022) for a detailed evaluation of nonclinical data. Labeling revisions addressed the weight management indication.

### Pharmacology

In vivo and in vitro studies, previously reviewed under NDA 215866, indicate that tirzepatide plays a role in lowering body weight and decreasing food consumption. In normal, fasted mice, subcutaneous administration of tirzepatide decreased the rate of gastric emptying. While a complex relationship exists between gastric emptying and appetite, decreased gastric motility has been linked with increased feelings of satiety and termination of food intake (Janssen P et al. 2011). When evaluated in rats fed a high fat/high sucrose diet and diet induced obese (DIO) mice, tirzepatide caused decreases in food intake and body weight. Subcutaneously administered tirzepatide also reduced fat mass, fat-free mass, plasma cholesterol, and increased metabolic rates to a greater extent when compared a GLP-1 receptor agonist in DIO mice. In vitro, tirzepatide stimulated cAMP production and lipolysis in mature adipocytes that express the GIPR and not the GLP-1R.

## 1.3 Recommendations

### 1.3.1 Approvability

The nonclinical data support market approval of tirzepatide as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults.

### 1.3.2 Additional Nonclinical Recommendations

None.

### 1.3.3 Labeling

Draft labeling revisions are indicated as of time of review finalization. During the first round of labeling negotiations, the following changes were proposed as indicated by tracked changes,

**Figure 1: Percent Body Weight Loss after Exposure to a GLP-1 receptor agonist or Tirzepatide**

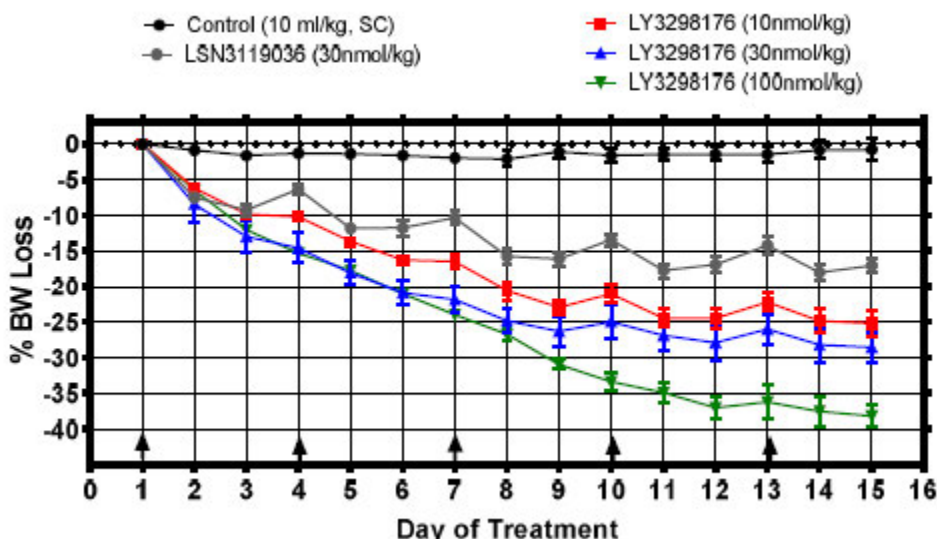


Figure was copied from the sponsor's submission (Figure 1 in Study Report # DBT206). Treatments were administered every three day on Days 1, 4, 7, 10, and 13 as illustrated with arrows. LSN3119036 (30 nmol/kg/every 3 days) is a GLP-1 analogue. LY3298176 is tirzepatide. Values are presented as mean ± SEM with n = 5.

**Figure 2: Cumulative Food Intake after Exposure to a GLP-1 receptor agonist or Tirzepatide**

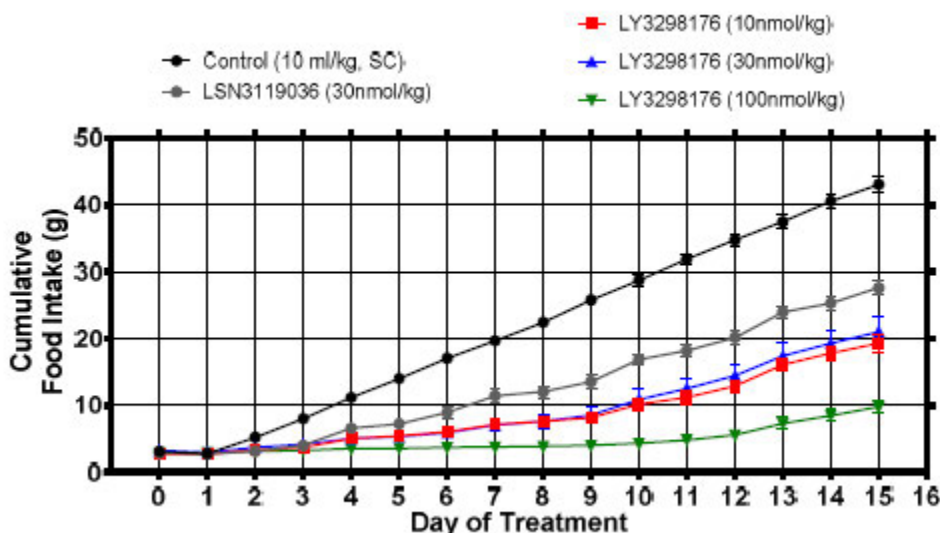


Figure was copied from the sponsor's submission (Figure 2 in Study Report # DBT206). Treatments were administered every three day on Days 1, 4, 7, 10, and 13 as illustrated with arrows. LSN3119036 (30 nmol/kg/every 3 days) is a GLP-1 analogue. LY3298176 is tirzepatide. Values are presented as mean ± SEM with n = 5.

The applicant was asked to provide clarification describing the nonclinical data that was used to support the statement that (b) (4) The applicant

noted that indirect calorimetry studies show a decreased respiratory exchange ratio (RER) in diet-induced obese mice subcutaneously administered 30 nmol/kg tirzepatide every 3 days for 22 days. The decreased RER persisted for approximately 8 days after the first dose of tirzepatide when decreases in food consumption were greatest. <sup>(b) (4)</sup>

this finding was transient persisting only after the first two doses. Therefore, the nonclinical team does not believe there is adequate support for the following sentence to be included in labeling and recommends that it be removed. <sup>(b) (4)</sup>

**Figure 3: The effect of chronic treatment with tirzepatide on respiratory exchange ratio in DIO mice**

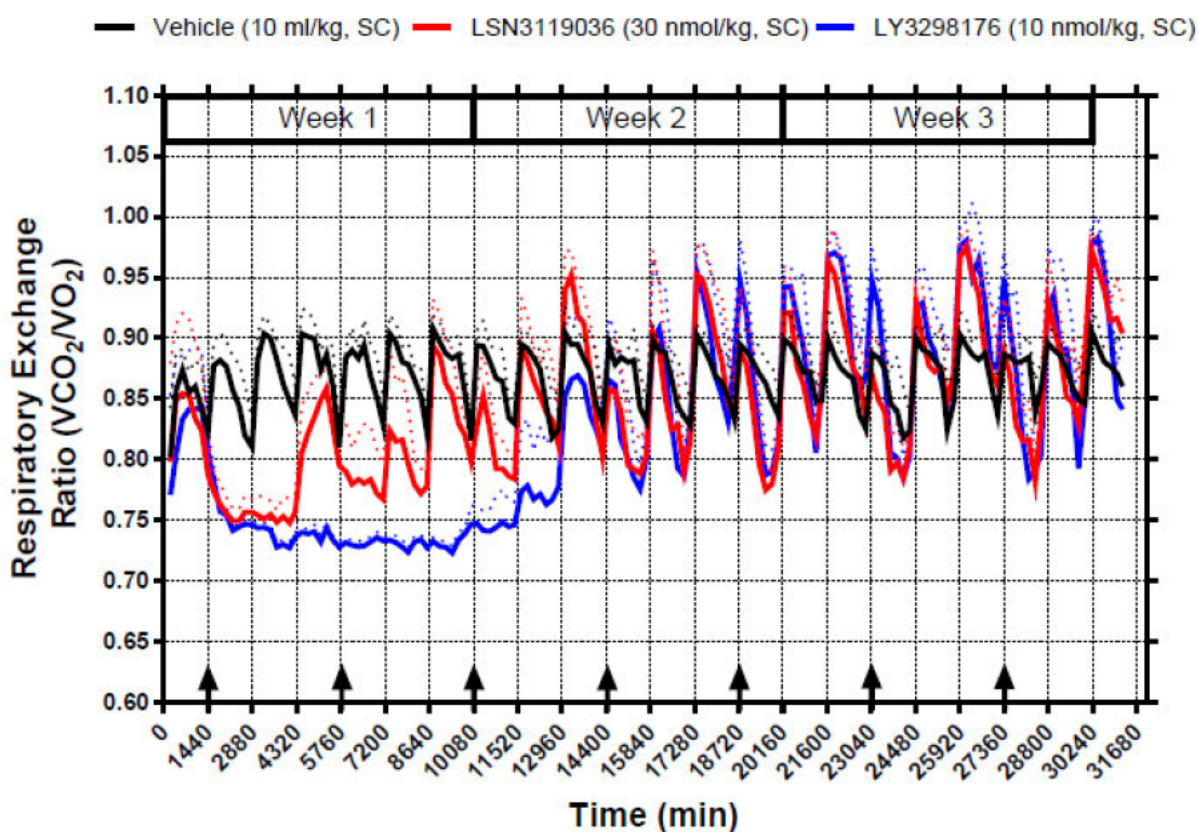


Figure copied from the sponsor's submission (Figure 9 from Study Report DBT206). Black: 20 mM Citrate Buffer at pH 7.0, Red: LSN3119036 or semaglutide (30 nmol/kg), Blue: Tirzepatide or LY3298176 (10 nmol/kg)

## 2 Drug Information

### 2.1 Drug

CAS Registry Number (Optional)  
2023788-19-2

**Generic Name**

Tirzepatide

**Code Name**

LY3298176, AD-60212, ALN-60212, ALN-PCSSC, PCSSC

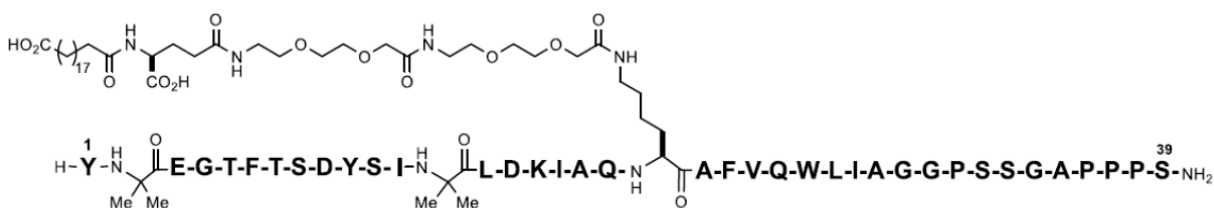
**Chemical Name**

L-Serinamide, L-tyrosyl-2-methylalanyl-L- $\alpha$ -glutamylglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L- $\alpha$ -aspartyl-L-tyrosyl-L-seryl-L-isoleucyl-2-methylalanyl-L-leucyl-L- $\alpha$ -aspartyl-L-lysyl-L-isoleucyl-L-alanyl-L-glutamyl-L-N6-[(2S)-22,42-dicarboxy-1,10,19,24-tetraoxo-3,6,12,15-tetraoxa-9,18,23-triazadotetracont-1-yl]-L-lysyl-L-alanyl-L-phenylalanyl-L-valyl-L-glutamyl-L-tryptophyl-L-leucyl-L-isoleucyl-L-alanyl-glycylglycyl-L-prolyl-L-seryl-L-serylglycyl-L-alanyl-L-prolyl-L-prolyl-L-prolyl

**Molecular Formula/Molecular Weight** $C_{225}H_{348}N_{48}O_{68}$ 

4810.52 Da (monoisotopic mass)

4813.45 Da (average mass IUPAC 2007)

**Structure or Biochemical Description**

LY3298176 or tirzepatide is a 39-amino acid synthetic peptide. It consists of a peptide component based on the GIP sequence containing 2 non-coded amino acids (aminoisobutyric acid, Aib) in positions 2 and 13, a C-terminal amide, and the Lys residue at position 20 is attached to a 1,20-eicosanedioic acid via a linker which consists of a  $\gamma$ -Glu and two 8-amino-3,6-dioxaoctanoic acids. The secondary structure of tirzepatide is predominantly  $\alpha$ -helical, the tertiary structure is consistent with a natively folded peptide, and tirzepatide reversibly self-associates with a monomer-trimer-hexamer equilibrium under native conditions.

**Pharmacologic Class**

Glucose-dependent insulintropic polypeptide receptor agonist and glucagon-like peptide 1 receptor agonist

**2.2 Relevant INDs, NDAs, BLAs and DMFs**Tirzepatide for subcutaneous injection

IND 128801: treatment of type 2 diabetes mellitus

IND 139721: treatment of obesity, chronic weight

(b) (4)

(b) (4)

NDA 215866: adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

## 2.3 Drug Formulation

**Table 1: Composition of Tirzepatide Injection**

| Ingredient                            | Quantity (mg) per Syringe |             |               |              |                |              | Function          | Reference to Standards               |
|---------------------------------------|---------------------------|-------------|---------------|--------------|----------------|--------------|-------------------|--------------------------------------|
|                                       | 2.5 mg/0.5 mL             | 5 mg/0.5 mL | 7.5 mg/0.5 mL | 10 mg/0.5 mL | 12.5 mg/0.5 mL | 15 mg/0.5 mL |                   |                                      |
| <b>Active Ingredient</b>              |                           |             |               |              |                |              |                   |                                      |
| Tirzepatide                           | 2.5                       | 5           | 7.5           | 10           | 12.5           | 15           | Active ingredient | See Section 3.2.S.4.1, Specification |
| <b>Other Ingredients</b>              |                           |             |               |              |                |              |                   |                                      |
| Dibasic Sodium Phosphate Heptahydrate | (b) (4)                   |             |               |              |                |              | (b) (4)           | USP-NF                               |
| Sodium Chloride                       | (b) (4)                   |             |               |              |                |              | (b) (4)           | USP-NF, Ph.Eur.                      |
| Hydrochloric Acid Solution, (b) (4)   | (b) (4)                   |             |               |              |                |              | pH adjustment     | USP-NF, Ph.Eur.                      |
| Sodium Hydroxide Solution, (b) (4)    | (b) (4)                   |             |               |              |                |              | pH adjustment     | USP-NF, Ph.Eur.                      |
| Water for Injection                   | (b) (4)                   |             |               |              |                |              | Vehicle           | USP-NF, Ph.Eur.                      |

Abbreviations: Ph.Eur. = European Pharmacopoeia; q.s. = quantity sufficient; USP-NF = United States Pharmacopoeia National Formulary

Table copied from the sponsor's submission (Table 3.2.P.1.2-1)

## 2.4 Comments on Novel Excipients

There are no novel excipients in the tirzepatide (LY3298176) formulation.

## 2.5 Comments on Impurities/Degradants of Concern

All impurities/degradants present in the drug product are considered to be reasonably safe and have been previously discussed under NDA 215866.

## 2.6 Proposed Clinical Population and Dosing Regimen

The recommended starting dosage of ZEPBOUND in adults is 2.5 mg injected subcutaneously once weekly. After 4 weeks, increase the dosage to 5 mg injected subcutaneously once weekly. The dosage may be increased in 2.5 mg increments, after at least 4 weeks on the current dose. The recommended maintenance dosages of ZEPBOUND in adults are 5 mg, 10 mg, or 15 mg injected subcutaneously once weekly. The maximum dosage of ZEPBOUND is 15 mg injected subcutaneously once weekly.

## 2.7 Regulatory Background

On November 17, 2022, Eli Lilly and Co. submitted an original new drug application (NDA) for tirzepatide (also known as Zepbound) for use as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults.

## 3.3 Previous Reviews Referenced

NDA 215866, Elena Braithwaite, 03/16/2022

IND 128801, Elena Braithwaite, 10/13/2022

## 12 Appendix/Attachments

### References

1. Janssen P, Vanden Berghe P, Verschueren S, Lehmann A, Depoortere I, Tack J. Review article: the role of gastric motility in the control of food intake. *Aliment Pharmacol Ther.* 2011 Apr;33(8):880-94. doi: 10.1111/j.1365-2036.2011.04609.x. Epub 2011 Feb 22. PMID: 21342212.

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/s/  
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