Cross-Discipline Team Leader
Summary Review for Regulatory Action

Date	(electronic stamp)
From	Laura Higginbotham, MD, MPH
Subject	Cross-Discipline Team Leader Summary Review
NDA/BLA # and Supplement#	NDA 215256, S-015
Applicant	Novo Nordisk Inc.
Date of Submission	January 29, 2024
PDUFA Goal Date	November 29, 2024
Proprietary Name	Wegovy
Established or Proper Name	Semaglutide
Dosage Form(s)	Injection
Applicant Proposed Indication(s)/Population(s)	WEGOVY is indicated in combination with a reduced calorie diet and increased physical activity: • to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight. • to reduce excess body weight and maintain weight reduction long term in: o Adults and pediatric patients aged 12 years and older with obesity o Adults with overweight in the presence of at least one weight-related comorbid condition.
Applicant Proposed Dosing Regimen(s)	The maintenance dosage of WEGOVY is either 2.4 mg (recommended) or 1.7 mg once-weekly. Consider treatment response and tolerability when selecting the maintenance dosage *[see Clinical Studies (14.1)]*.
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	WEGOVY is indicated in combination with a reduced calorie diet and increased physical activity: • to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight. • to reduce excess body weight and maintain weight reduction long term in:

	o Adults and pediatric patients aged 12 years and older with obesity o Adults with overweight in the presence of at least one weight-related comorbid condition.
Recommended Dosing Regimen(s) (if applicable)	The maintenance dosage of WEGOVY is either 2.4 mg (recommended) or 1.7 mg once weekly. Consider treatment response and tolerability when selecting the maintenance dosage *[see Adverse Reactions (6.1), Clinical Studies (14.2, 14.3)]*.

1. Background

Semaglutide (Wegovy) is a GLP-1 receptor agonist originally approved in June 2021 for chronic weight management in adults with obesity/overweight. Wegovy's current USPI contains the following indications:

> WEGOVY is indicated in combination with a reduced calorie diet and increased physical activity:
>
> - To reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight.
> - To reduce excess body weight and maintain weight reduction long term in:
>   - Adults and pediatric patients aged 12 years and older with obesity
>   - Adults with overweight in the presence of at least one weight-related comorbid condition.

Semaglutide is also marketed in the US as Ozempic (NDA 209637) at doses of 0.5 mg, 1 mg, and 2 mg SC once weekly and as Rybelsus (NDA 213051) oral (PO) tablet, at doses of 7 mg and 14 mg once daily for glycemic control in adults with type 2 diabetes. Ozempic also has an indication to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes and established cardiovascular disease.

Wegovy's indications for weight reduction in adults (approved June 2021) and pediatric patients aged 12 years and older (approved December 2022) were originally labeled for use at a single maintenance dose of 2.4 mg subcutaneous (SC) weekly. In July 2023, a supplemental New Drug Application (sNDA) was approved to add 1.7 mg SC weekly as an additional maintenance dose in adults based on the results of a single adequate and well-controlled trial conducted outside the US plus confirmatory evidence. The new dosing regimen triggered PREA, and the Applicant was issued PMR 4472-1 (below), to determine whether 1.7 mg SC weekly should also be added as an additional maintenance dose in pediatric patients.

> PMR 4472-1: Conduct exposure and exposure-responses analyses to evaluate the efficacy and safety of semaglutide to support the 1.7 mg dose for the treatment of chronic weight management in pediatric patients with obesity ages 12 to less than 18 years. In addition to pharmacokinetic and pharmacodynamic data from STEP 1 and STEP TEENS, include data from STEP 6 in your analyses.

To satisfy PMR 4472-1, the Applicant submitted this sNDA, supported by the results of a study entitled, "Extrapolation of Pharmacokinetics, Efficacy and Safety from 2.4 mg to 1.7 mg Semaglutide in Adolescents, Using Population PK and Exposure-Response." Based on the study results, the Applicant proposes to update the USPI with an additional maintenance dose of 1.7 mg in pediatric patients with obesity ages 12 to <18 years.

This review serves as the Cross-Discipline Team Leader (CDTL) review and the Decisional Memo. It summarizes the major issues related to approvability and labeling of the sNDA. All

review disciplines recommend approval. For additional details, refer to the individual discipline reviews and consult reviews referenced in this document.

2. Product Quality

The Applicant did not submit any new Chemistry, Manufacturing, and Controls (CMC) information with the supplement.

3. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were submitted or required for this sNDA.

4. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP), consisting of clinical pharmacology and pharmacometrics reviewers, reviewed the results of the pharmacometrics extrapolation study report entitled, "Extrapolation of pharmacokinetics, efficacy and safety from 2.4 mg to 1.7 mg semaglutide in adolescents, using population PK and exposure-response analysis." OCP conducted simulation analyses to support extrapolation of prior adult clinical data (1.7 mg and 2.4 mg SC weekly) and prior pediatric clinical data (2.4 mg SC weekly) to approval of 1.7 mg SC weekly as an additional maintenance dose in pediatrics. Simulation analyses were based on population PK modeling and exposure-response (E-R) analyses for efficacy and safety. The team determined that extrapolation supports the proposed prescribing information for the additional maintenance dose (1.7 mg once weekly) in pediatric patients 12 years and older.

Model-predicted efficacy results from baseline to Week 68 for placebo, 1.7 mg, and 2.4 mg dosages in pediatric patients 12 years and older are displayed in the table below, along with observed results for the 2.4 mg dosage in STEP TEENS (the single adequate and well-controlled trial that formed the basis of the Wegovy 2.4 mg approval in pediatric patients aged 12 years and older).

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	Model-Predicted			**Observed[1]**
Baseline to Week 68	**Placebo**	**1.7 mg SC weekly**	**2.4 mg SC weekly**	**2.4 mg SC weekly**
Mean (95% CI) percent change in body weight	1.44% (-3.68, 5.65)	-13.4% (-17.7, -8.96)	-15.6% (-20.0, -10.8)	-14.7%
Mean (95% CI) percent change in BMI	0% (-4.01, 3.79)	-15.2% (-18.8, -11.4)	-17.4% (-21.4, -13.4)	-16.1%
% of patients (95% CI) achieving ≥5% BMI reduction	27.2% (10.4, 46.3)	79.6% (68.7, 88.8)	83.7% (73.9, 91.8)	77.1%

[1] Trial STEP TEENS, treatment policy estimand

Because the model-predicted treatment effect for semaglutide 2.4 mg SC weekly in adolescents is consistent with the actual observed treatment effect of 2.4 mg SC weekly in the STEP TEENS clinical trial, it is reasonable to assume that the model would behave similarly in predicting the treatment effect of semaglutide 1.7 mg SC weekly in adolescents.

The OCP team also performed exposure exposure-safety analyses for nausea and vomiting. Refer to their review for details. The modeling supports the safety of semaglutide 1.7 mg SC weekly in adolescents.

The Office of Clinical Pharmacology (OCP) team reviewed the submitted datasets and reports, reached agreement with the Applicant on the revised label, and considers PMR 4472-1 fulfilled. I concur with their recommendation. Refer to the OCP review for details of the review.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical- Efficacy

No new clinical data were submitted or required for this supplemental NDA.

The model-predicted treatment effect of -15.2% reduction in BMI is clinically meaningful and supports inclusion of 1.7 mg SC weekly as an additional maintenance dose for adolescent patients with obesity.

7. Safety

No new clinical data were submitted or required for this supplemental NDA.

Approval of semaglutide 1.7 mg in adults did not identify any new safety issues. Considering the clinical experience with 2.4 mg once weekly in both adult and adolescent patients, a reduced maintenance dose of 1.7 mg once weekly is expected to be safe in adolescent patients and is further supported by exposure-safety analyses performed by the Applicant and OCP.

8. Advisory Committee Meeting

No advisory committee (AC) meeting was conducted for this application.

9. Pediatrics

“Extrapolation of pharmacokinetics, efficacy and safety from 2.4 mg to 1.7 mg semaglutide in adolescents, using population PK and exposure-response analysis” was submitted in response to PREA PMR 4472-1. “Extrapolation of pharmacokinetics, efficacy and safety from 2.4 mg

to 1.7 mg semaglutide in adolescents, using population PK and exposure-response analysis" is completed and fulfills PMR 4472-1.

10. Labeling

Prescribing Information
The Applicant submitted draft labeling related to the additional pediatric maintenance dose. This section describes important additions and omissions agreed upon during labeling negotiations.

- DOSAGE AND ADMINISTRATION:
  - Inclusion of 1.7 mg semaglutide as an additional maintenance dosage for pediatric patients
- Safety information in the BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS:
  - Revisions to acute pancreatitis W&P
  - Addition of new W&P for severe gastrointestinal reactions

11. Postmarketing Recommendations

No REMS or additional PMRs or PMCs are required for approval of this supplemental application.

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/

LAURA B HIGGINBOTHAM
11/26/2024 08:11:25 PM

JOHN M SHARRETTS
11/26/2024 10:55:06 PM
I concur.