CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213051Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 213051 and 213182
Review 1

Drug Name/Dosage Form	Rybelsus (semaglutide) tablets
Strength	3 mg, 7 mg, or 14 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Novo Nordisk
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original and amendments (NDA 213051)	Original submission (3/20/2019) and amendments (5/23/19, 6/28/19, 7/02/29, 7/05/19, 7/29/19, 8/01/19, and 8/15/19).	Quality modules 3, 1.14 and 1.11
Original and amendments (NDA 213182)	Original submission (3/20/2019)	Quality modules 1.4 and 1.12.4

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Daniel Jansen	Branch II/New Drug API
Drug Product	Christopher Galliford	Branch VI/New Drug Products II
Process/Microbiology/Facility	Frank Wackes	Branch II/ Inspectional Assessment/OPF
Regulatory Business Process Manager	Leeza Rahimi	Branch I/Regulatory Business Process Management I
Application Technical Lead	Muthukumar Ramaswamy	Branch VI/New Drug Products II
Environmental Analysis (EA)	Christopher Galliford	Branch VI/New Drug Products II

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	Adequate	12/14/2012 (Craig Bertha) and NDA 213051 review for drug product (8/8/19)	LOA 1/10/2019

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	114464	Semaglutide tablets

2. CONSULTS: None

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER

Executive Summary

I. Recommendations and Conclusion on Approvability

The recommendation from the Office of Pharmaceutical Quality (OPQ) for NDA 213051 and 213182 is approval. This recommendation includes acceptable recommendation for the facilities listed in the application.

II. Summary of Quality Assessments

A. Product Overview

Semaglutide is a long-acting analogue of GLP-1 molecule and is currently marketed as Ozempic (semaglutide) injection for improving glycemic control in adults with type 2 diabetes (NDA 209637). Novo Nordisk has submitted two new drug applications (NDA 213051 and NDA 213182) for the marketing approval of Rybelsus® (semaglutide) tablets. Rybelsus® tablets are intended for the following indications:

- Glycemic control in adults with type 2 diabetes (NDA 213051).
- To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes and established CV (b) (4) (NDA 213182).

Rybelsus tablets will be available as 3, 7, and 14 mg tablets. Rybelsus tablets are for once daily oral administration. Each strength tablets will be available in cartons containing 3 child-resistant blister cards of 10 tablets. Rybelsus® tablets should to be stored at temperature between 68ºF to 77ºF (20ºC to 25ºC).

Semaglutide tablets are co-formulated with 300 mg of salcaprozate sodium (SNAC, a permeation enhancer). The isoelectric point of the semaglutide is 5.4. The peptide has a low solubility at pH range 2-6. Semaglutide is considered a BCS class 4 molecule (low permeability and low solubility). It is hypothesized that SNAC facilitates the oral absorption of semaglutide in stomach either by transiently increasing the transcellular permeability in gastric epithelium or through buffering action on the local environment near the site of action to provide a high pH and thereby protecting the semaglutide from degradation.

All CMC information necessary to support NDA 213182 was cross-referenced to Module 2 and 3 of NDA 213051. Therefore, the CMC review provided for NDA 213051 was used to make the OPQ recommendation for NDA 213182.

Proposed Indication(s) including Intended Patient Population	*Glycemic control and CV risk reduction; Refer to CTDL memo*
Duration of Treatment	*Refer to CTDL memo*
Maximum Daily Dose	*14 mg*

Alternative Methods of Administration	*Not applicable*

B. Quality Assessment Overview

Drug Substance

Semaglutide is a modified analogue of human GLP-1 [7-37] peptide. Compared to the amino acid sequence of GLP-1 [7-37] peptide, the semaglutide peptide sequence contains two amino acid substitutions (Ala8 to Aib8 (2-aminoisobutyric acid), Lys34 to Arg34) and a modification at lysine 26 side chain with fatty diacid moiety. The manufacturing process for semaglutide drug substance consists of (b) (4) The drug substance batches produced from the proposed drug substance manufacturing process (process III) was used in Phase 1 and 3 clinical studies.

The CMC information for drug substance was reviewed by Dr. Daniel Jansen. Dr. Jansen's review concluded that the NDA contains adequate information on drug substance characterization and provides adequate manufacturing process description, process controls, and drug substance specification for manufacturing consistent quality drug substance. Based on stability data review, a shelf-life of (b) (4) months is granted for the semaglutide drug substance when stored (b) (4) For additional details, please refer to CMC review for drug substance in Panorama dated 5/28/2019.

Drug Product

Semaglutide tablets will be available in 3 strengths (3 mg, 7 mg, or 14 mg per tablet), as white to light yellow oval shaped tablets debossed with "novo" on one side and on the other side with 3 or 7 or 14. The tablets are packaged in blister cards (b) (4) Each blister card will contain 10 tablets. Blister packs are further packaged in cartons (3 per carton).

Each strength tablet contains 300 mg of salcaprozate sodium. Besides salcaprozate sodium (SNAC), the tablets contain micro-crystalline cellulose (b) (4), Povidone (b) (4), and magnesium stearate (b) (4). Salcaprozate is a novel excipient. All other excipients present in the drug product are USP grade excipients.

Excipient related information including manufacturing and control information for salcaprazoate was reviewed by drug product reviewer. His review concluded that the manufacturing and control information for SNAC and other excipients are adequate. The proposed specifications for salcaprozate include (b) (4)

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