CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-341

CHEMISTRY REVIEW(S)

MEMORANDUM

Date: 04-Aug-2009

From: Joseph Leginus, Review Chemist, Branch II/DPA I/ONDQA

To: NDA 22-341 Victoza® (liraglutide (rDNA origin) injection)

Subject: Single, multi-dose (1.2 mg/1.8 mg) injector pen

Background:

- On December 19, 2009, Novo Nordisk submitted an amendment to NDA 22-341 describing an alternate pen configuration that would allow patients to use a single pen to inject each of the recommended doses (0.6, 1.2, 1.8 mg) of Victoza (liraglutide rDNA) injection).
- b(4)

Reviewer's Comments:

- b(4)
- . The draft labeling is the same as the previously submitted labeling with the additional pen configuration included.
- Dose accuracy study data was provided showing acceptable performance of the new pen at the three dose levels (0.6, 1.2, 1.8 mg).
- b(4)

Conclusion:

There are no CMC issues related to Novo Nordisk's alternate pen configuration for Victoza, a single, multi-dose (1.2 mg/1.8 mg) pen.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22341	ORIG 1		VICTOZA (LIRAGLUTIDE)

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/s/

JOSEPH M LEGINUS
08/04/2009

ALI H AL HAKIM
08/04/2009

Victoza®
Liraglutide Injection
NDA 22-341

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Novo Nordisk, Inc.
100 College Road West,
Princeton, NJ 08540

Indication: Liraglutide is indicated as an adjunct to diet and exercise to achieve glycemic control in patients with type 2 diabetes mellitus

Presentation: Liraglutide injection is a parenteral drug product for once daily subcutaneous self-administration. It is supplied in multiple-dose pre-filled pen-injectors containing 3 mL of drug product at a concentration of 6 mg/mL. [redacted] :

b(4)

EER Status: Acceptable, 23-Mar-2009

Consults: EA – Categorical exclusion granted
CDRH - Completed, S. Syad, 13-Feb-2009
Methods Validation – Revalidation by Agency was not requested
Microbiology – Acceptable, B. Riley, 4-Mar-2009

Original Submission: 23-May-2008

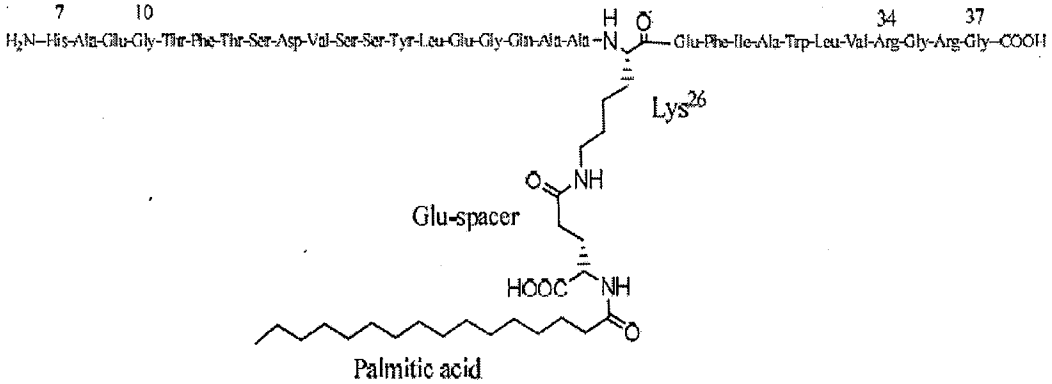
Re-submissions: N/A

Post-Approval CMC Agreements: None beyond the typical stability commitments.

Drug Substance:

Liraglutide is a fragment of the naturally occurring human GLP-1 (Glucagon-like peptide-1) sequence position 7-37 having two modifications: 1) substitution of the naturally occurring lysine amino acid residue in position 34 by arginine, and 2) addition of a glutamic acid-spaced palmitic acid to the ε-amino group of lysine in position 26. Liraglutide precursor is produced using recombinant DNA technology in yeast (*Saccharomyces cerevisiae*). The chemical name of liraglutide is

glycine, L-histidyl-L-alanyl-L-α-glutamylglycyl-Lthreonyl-L-phenylalanyl-L-threonyl-L-seryl-L-α-aspartyl-L-valyl-L-seryl-L-seryl-L-tyrosyl-L-leucyl-L-α-glutamylglycyl-Lglutaminyl-L-alanyl-L-alanyl-N6-[N-(1-oxohexadecyl)-L-γ-glutamyl]-L-lysyl-L-α-glutamyl-Lphenylalanyl-L-isoleucyl-L-alanyl-L-tryptophyl-L-leucyl-L-valyl-L-arginylglycyl-L-arginyl-. The chemical structure, molecular formula and molecular weight are provided below:



The molecular formula of liraglutide is $C_{172}H_{265}N_{43}O_{51}$ with a molecular weight of 3751.20.

Liraglutide precursor is produced by recombinant DNA technology form yeast *Saccharomyces cerevisiae.* The manufacturing process is a — step process divided into three sections, fermentation, recovery, and purification. The purification process consists of purification of the liraglutide precursor, acylation of this precursor ——— and finally purification ——— of liraglutide. b(4)

The structure of liraglutide was elucidated by a variety of analytical and spectrophotometric techniques, including amino acid analysis (AAA), amino acid sequencing, mass spectrometry (MALDI-TOF MS), circular dichroism (CD) and peptide mapping.

The proposed release specifications include appearance, identification (peptide mapping and HPLC), content (HPLC), specific bioactivity (cAMP assay), individual peptide related impurities and total peptide related impurities (HPLC), ——— bacterial endotoxin, total viable count and host cell protein (ELISA). The proposed regulatory methods have been validated. b(4)

Reference standards for the API have been developed and characterized. Product related impurities structurally related to liraglutide generated during the fermentation, recovery, purification or storage of the drug substance have classified based on their RP-HPLC elution position relative to the drug substance. Process derived impurities originating from the liraglutide manufacturing process were not detected in the drug substance. A shelf life of 24 months will be granted for the drug substance when stored at -18°C ±2°C/ambient RH or lower temperatures based on real-time studies obtained from primary stability data.

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