CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206321Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 206321	Submission Date: 12/20/2013
Brand Name	Saxenda
Generic Name	Liraglutide
OCP Division	Clinical Pharmacology-2
OND Division	Metabolism and Endocrinology Products
Sponsor	Novo Nordisk
Submission Type, Code	NDA 505 (b) (1); Standard
Formulation; Strength(s)	Injection
Proposed Indication	For weight management in adult patients with an initial body mass index (BMI) of 30 kg/m^2 or greater or 27 kg/m^2 or greater in the presence of at least one weight related comorbidity
Clinical Pharmacology and Pharmacometrics Reviewer	Jayabharathi Vaidyanathan, Ph.D
Clinical Pharmacology TL	Immo Zadezensky, Ph.D
Pharmacometrics TL	Nitin Mehrotra, Ph.D

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology (DCP-2 and DPM) has reviewed the clinical pharmacology data submitted on 12/2013 under NDA 206321 and recommend approval from a clinical pharmacology perspective. An optional Inter-Division Level OCP briefing was held on September 17, 2014 to discuss this submission. Labeling comments are on pages 38-39.

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology Findings

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor analog with 97% amino acid sequence homology to human endogenous GLP-1. Liraglutide is approved to treat type 2 diabetes (T2DM) at doses up to 1.8 mg once a day (NDA 22-341). This current NDA application is proposing the use of liraglutide for weight management at doses of 3.0 mg once daily.

Refer to details of general clinical pharmacology information of liraglutide in clinical pharmacology review under NDA 22-341. This review will focus on the relevant clinical pharmacology information for the proposed indication.

According to the current proposed label, the proposed indication for liraglutide 3 mg is as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial Body Mass Index (BMI) of
- 30 kg/m^2 or greater (obese), or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight related comorbidity such as dysglycemia (pre-diabetes and type 2 diabetes mellitus), hypertension, dyslipidemia, or obstructive sleep apnea.

Similar to what is approved for T2DM population, to improve gastro-intestinal tolerability, for all patients, the starting dose is proposed to be 0.6 mg. The starting dose is then proposed to be increased to 3 mg with increments of 0.6 mg with at least one week intervals (i.e. 0.6, 1.2, 1.8, 2.4 and 3.0 mg). Treatment should be evaluated after a minimum of 12 weeks on the 3.0 mg dose to assess the treatment effect.

The clinical development program of liraglutide draws support from a clinical pharmacology study that evaluated the PK/PD of liraglutide in obese subjects, 1 Phase 2 dose ranging trial (1807) and two Phase 3 efficacy and safety trials (1839 and 1922).

Liraglutide pharmacokinetics (PK) and pharmacodynamics (PD) has been characterized following subcutaneous administration of 1.8 mg under the T2DM program and following 3.0 mg dose in obese subjects. Clinical pharmacology review of the information submitted under NDA 206321 revealed the following key findings:

Liraglutide PK:

The proposed drug product formulation of liraglutide (3.0 mg) used in the obesity development program is similar to the currently marketed formulation (1.8 mg). A population PK analysis was submitted under NDA 22-341 (Victoza) and for the current NDA for obesity (NDA 206321). The sponsor is referring to the data provided under the T2DM program to bridge clinical pharmacology and safety information (e.g., QT, and DDI).

Baseline body weight was the most significant covariate affecting the clearance (CL/F) of liraglutide as determined by the population PK analysis conducted for both programs.

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