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APPLICATION NUMBER:

206321Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	10 November 2014
From	James P. Smith, MD, MS
Subject	Summary Review for Regulatory Action
NDA#	206321
Applicant	Novo Nordisk
Date of Submission	20 December 2013
PDUFA Goal Date	20 October 2014
Proprietary Name / Established (USAN) names	SAXENDA / liraglutide
Dosage forms / Strength	Injectable solution, 6 mg/mL, to be administered subcutaneously at a maintenance dose of 3 mg daily via a pre-filled PDS290 pen injector
Proposed Indication	Chronic weight management
Recommended:	Approval

Material Reviewed/Consulted & Primary Reviewer(s)		
Medical Officer Review	18 Oct 2014	Julie Golden, MD
Statistical Review (Efficacy)	15 Sep 2014	Bradley McEvoy, DrPH
Statistical Review Addendum (Efficacy)	16 Oct 2014	Bradley McEvoy, DrPH
Statistical Review (CV Safety)	12 Sep 2014	Rongmei Zhang, PhD
Clinical Pharmacology Review	19 Sep 2014	Jayabharathi Vaidyanathan, PhD
QT-IRT Consult	21 Oct 2011	Zhu Hao
Study Endpoints Review	03 Oct 2014	Sarrit Kovacs, PhD
Epidemiology: Review of Clinical Trials	18 Aug 2014	Christian Hampp, PhD
Epidemiology: Review of Interim Study Report	30 Jun 2014	Christian Hampp, PhD
Division of Oncology Drug Products 1 Consult	03 Jul 2014	Jonathan P. Jarow, MD
Division of Neurology Products Consult	21 Oct 2014	Ronald Farkas, MD, PhD
Pharmacovigilance Review	13 Aug 2014	Debra L. Ryan, PharmD, MBA & Carolyn J. Tabak, MD, MPH
Clinical Review of Post-marketing MTC Cases	26 Sep 2014	Marina Zemskova, MD
CMC Review	14 May 2014	Joseph Leginus, PhD
Microbiology Review	16 Jan 2014	Bryan S. Riley, PhD
Pharmacology/Toxicology Review	15 Sep 2014	Anthony L. Parola, PhD
REMS Modification Review #1	26 Sep 2014	Amarilys Vega, MD, MPH & Kate Oswell, MA
REMS Modification Review #2	16 Oct 2014	Amarilys Vega, MD, MPH & Kate Oswell, MA
Clinical Inspection Summary/OSI	02 Sep 2014	Cynthia F. Kleppinger, MD
CDRH Human Factors Review	22 Aug 2014	QuynhNhu Nguyen
CDRH Device Review	16 Apr 2014	Sajjad H. Syed
CDRH Office of Compliance	30 Apr 2014	LCDR John W. Diehl
OSE/DMEPA Human Factors & Labeling Rev.	22 Jul 2014	Sarah K. Vee, PharmD
OSE/DMEPA Proprietary Name Review	01 Apr 2014	Sarah K. Vee, PharmD
OPDP Labeling Consult	14 Aug 2014	Kendra Y. Jones
DMPP/OPDP Patient Labeling Review	15 Oct 2014	Sharon W. Williams, MSN, BSN, RN (DMPP) & Kendra Y. Jones (OPDP)

QT-IRT: QT Interdisciplinary Review Team; MTC: Medullary thyroid cancer; CMC: Chemistry, Manufacturing, and Controls; REMS: Risk Evaluation and Mitigation Strategy; OSI: Office of Scientific Investigations; CDRH: Center for Devices and Radiological Health; OSE: Office of Surveillance and Epidemiology; DMEPA: Division of Medication Error Prevention and Analysis; OPDP: Office of Prescription Drug Promotion; DMPP: Division of Medical Policy Programs

1. INTRODUCTION

In the present application, the applicant has proposed that "Saxenda is indicated 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 one weight related comorbidity such as hypertension, dysglycemia (prediabetes and type 2 diabetes mellitus), dyslipidemia or obstructive sleep apnea."

This review summarizes the conclusions and regulatory recommendations of the review disciplines assigned to review the safety and efficacy of Saxenda (liraglutide 3 mg for injection) for chronic weight management. I am not aware of any disagreements within or between the review disciplines regarding final regulatory recommendations; all disciplines have recommended approval.

2. BACKGROUND

During the past two decades, there has been a dramatic increase in obesity in the United States. More than one-third (nearly 79 million) of U.S. adults and approximately 17% of children and adolescents have obesity according to the Centers for Disease Control and Prevention (CDC). Obesity is associated with increased risk for all-cause and cardiovascular mortality, and having obesity raises the risk of morbidity from hypertension, dyslipidemia, type 2 diabetes mellitus, cardiovascular disease, gallbladder disease, osteoarthritis, and sleep apnea. Although a comprehensive program of dietary strategies and lifestyle intervention/counseling is of paramount importance for affected individuals,[1] it is well recognized that these efforts are often insufficient to achieve health outcome goals.

Despite the extraordinarily adverse impact of overweight and obesity on patients and the healthcare system, there is a paucity of approved pharmacologic interventions to aid the treatment of obesity. The currently available FDA-approved medications for chronic weight management are Xenical (orlistat; approved in 1999), Belviq (lorcaserin HCl; 2012), Qsymia (phentermine/topiramate XR; 2012), and Contrave (naltrexone HCl/bupropion HCl; 2014).

Liraglutide is a human glucagon-like peptide 1 (GLP-1) analog that was approved 25 January 2010, under the tradename Victoza at a maximum dosage of 1.8 mg daily, for the treatment of type 2 diabetes mellitus (T2DM). During clinical trials designed to support approval for T2DM, it was noted that liraglutide appeared to reduce body weight, and the sponsor held a pre-IND/end-of-phase 2 meeting with the Division in March 2008 to discuss the development of liraglutide for weight management. It bears mention that the target population with overweight/obesity far surpasses the estimated 29 million people in the United States with diabetes.

Victoza was approved with a boxed warning to notify prescribers that the drug causes thyroid C-cell tumors at clinically relevant exposures in both rats and mice; the human relevance of this observation had not, and has still not, been determined by clinical or nonclinical studies. Given the strength of this nonclinical signal, however, it was determined that the benefit/risk of Victoza for the treatment of T2DM could only be favorable if approved with a Risk Evaluation and Mitigation Strategy (REMS), which comprises a communication plan and a timetable of assessments. The REMS also aimed to inform patients and providers about the risk of acute pancreatitis (including necrotizing pancreatitis).

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[1] Jensen MD, *et al.* 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation* 2014 Jun 24; 129(25 Suppl 2):S102-38.

3. CMC / DEVICE

CMC

Dr. Leginus conducted the CMC review for Saxenda. The drug products of the current NDA (Saxenda) and the previously approved Victoza (liraglutide [rDNA] injection; NDA 22341) have the same drug substance, [redacted] (b) (4). Both NDAs use an identical 3-mL glass cartridge as the primary container closure system, although the glass cartridge for Saxenda will be provided in a different pen injector (PDS290).

Dr. Leginus recommends approval from a CMC perspective. He has no recommendations for post-marketing commitments, agreements, or risk management steps. I concur with his assessment.

Microbiology

Dr. Riley noted that the proposed drug product is identical to an approved drug product from a product quality microbiology perspective and, therefore, no additional product quality microbiology assessment is necessary.

Facilities Review/Inspection

The facilities report from the Office of Compliance states that the overall recommendation is acceptable.

Device Review

The primary packaging for Saxenda is the same as that approved for Victoza under NDA 22341, i.e., a 3-mL cartridge, [redacted] (b) (4) The secondary packaging is an assembled PDS290 pen injector, which is a pre-filled, multiple-dose, disposable, delivery device that contains the 3-mL cartridge. The PDS290 liraglutide 3 mg pen injector is based on the approved FlexTouch® pen injector.

Device-related requests for information were conveyed to the applicant in the filing communication dated 04 March 2014. The applicant's responses, received 21 March 2014, were reviewed by Sajjad Syed (Electrical Engineer, CDRH General Hospital Devices Branch) and LCDR John W. Diehl (Regulatory Operations Officer, CDRH Office of Compliance, Division of Manufacturing and Quality) and found to be adequate. Dr. Patricia Beaston, an endocrinologist with CDRH's General Hospital Devices Branch, reviewed dose accuracy for the device as well (referenced in S. Syed's memo). CDRH indicated that there were no additional questions regarding device biocompatibility, safety, or performance.

Human Factors

QuynhNhu Nguyen reviewed a 129-subject human factors validation study from the CDRH perspective and identified concerns regarding needle stick injury and use errors that could result in mis-dosing.

Dr. Vee also reviewed this study from the DMEPA perspective. She noted that although some untrained users encountered difficulties while administering this product, the same difficulties "have also been reported with the use of other prefilled injection pen devices and have been managed reasonably well through labeling." She states that failure to perform these tasks would result in underdoses in most instances and would not be expected to cause serious harm acutely. This same pen-injector platform (PDS290) has been approved for Novolog and Levemir. Recommendations to improve labeling were provided.

I do not believe that there are outstanding issues related to human factors that would preclude approval with appropriate labeling.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

Dr. Anthony Parola reviewed the nonclinical data supporting this application, which cross-referenced pivotal nonclinical studies that were previously reviewed (by Dr. Parola) under Victoza NDA 22341. See Dr. Parola's review for a thorough discussion of the nonclinical data.

The proposed dosage for Saxenda is 3 mg/day, compared with the recommended maximum dosage of 1.8 mg/day for Victoza for the treatment of type 2 diabetes mellitus (T2DM). Because systemic clearance of subcutaneously injected liraglutide increases with body weight in humans, however, systemic exposure at steady state in obese adults administered 3 mg/day was only slightly higher than that in healthy adults administered 1.8 mg/day ($AUC_{0\text{-}24h}$ 854 vs. 809 nM·h) despite the 1.7-fold higher dose. Thus, Dr. Parola notes that "human exposure multiples based on systemic exposure for findings in nonclinical safety studies of liraglutide, including carcinogenicity and reproductive and developmental toxicity studies, are similar for 3.0 mg/day liraglutide in obese adults and 1.8 mg/day liraglutide in healthy adults."

Safety and toxicity of liraglutide were evaluated in safety pharmacology studies, single- and repeat-dose toxicity studies, genetic toxicity studies, 2-year carcinogenicity studies in rats and mice, reproductive and developmental toxicity studies, local tolerance studies, and mechanistic studies of liraglutide-induced thyroid C-cell tumors in rodents. All pivotal nonclinical safety studies were reviewed under Victoza NDA 22341. Dr. Parola summarizes that liraglutide toxicity occurred in thyroid (mice and rats) and at injection sites (mice, pigs, and monkeys), and included a mild anemia (mice, rats, and monkeys).

Carcinogenicity

Two-year lifetime carcinogenicity studies in mice and rats showed that liraglutide causes thyroid C-cell tumors at clinically relevant exposures in male and female mice and rats, as well as fibrosarcomas on the dorsal skin and subcutis of male mice. Thyroid C-cell tumors are rare findings during carcinogenicity testing in mice and rats. The nonclinical data regarding thyroid C-cell tumors, as summarized in the FDA briefing document for the 11 September 2014 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC), are presented below. Note that the no observed adverse effect level (NOAEL) for thyroid C-cell tumors in mice was 0.2 mg/kg/day liraglutide (1.8-times human exposure based on AUC comparison); a NOAEL was not established in the rat carcinogenicity study. These nonclinical data regarding thyroid C-cell tumors formed the basis for a boxed warning and Risk Evaluation and Mitigation Strategy (REMS) for Victoza. The approved labeling for Victoza and the proposed labeling for Saxenda state that it is unknown whether liraglutide will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC) in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors could not be determined by clinical or nonclinical studies.

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