

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206321Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

## Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF DRUG EVALUATION II  
DIVISION OF METABOLISM AND ENDOCRINOLOGY PRODUCTS

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**NDA/BLA #s:** NDA 206321  
**Products:** SAXENDA (liraglutide [rDNA origin] injection), solution for subcutaneous use  
**APPLICANT:** Novo Nordisk  
**FROM:** Jennifer Rodriguez Pippins, M.D., M.P.H.  
**DATE:** October 10, 2014

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Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

SAXENDA (liraglutide) is a subcutaneous injection for chronic weight management in addition to a reduced-calorie diet and physical activity. It will be approved for use in adults with a body mass index (BMI) of 30 or greater (obesity) or adults with a BMI of 27 or greater (overweight) who have at least one weight-related condition such as hypertension, type 2 diabetes, or high cholesterol (dyslipidemia). Liraglutide received initial U.S. approval in 2010 at a lower dose (1.8 mg vs 3.0 mg) as VICTOZA, a second-line therapy for the treatment of type 2 diabetes mellitus. VICTOZA (liraglutide) has in place a REMS (communication plan and a timetable for submission of assessments) that addresses the potential risk of medullary thyroid carcinoma and the risk of acute pancreatitis associated with VICTOZA (liraglutide).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for SAXENDA (liraglutide) to ensure that the benefits of the drug outweigh:

- The potential risk of medullary thyroid carcinoma identified in non-clinical studies of SAXENDA (liraglutide) and other glucagon-like peptide (GLP)-1 receptor agonists; and
- The risk of acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis, identified in the post-marketing reports for liraglutide. Cases of acute

pancreatitis have also been described in association with SAXENDA (liraglutide) during clinical trials. In reaching this determination, we considered the following:

- A. In 2011-2012 the prevalence of obesity in the United States was 34.9% in adults, and more than two-thirds of adults are either overweight or obese.<sup>1</sup> In 2011, approximately 2.74 million patients used antiobesity drugs; the most commonly used product was phentermine, which is approved for short-term weight loss.<sup>2</sup>
- B. Obesity is associated with numerous co-morbidities, including dyslipidemia, coronary artery disease, hypertension, stroke, and type 2 diabetes mellitus.
- C. The benefit of SAXENDA (liraglutide) is expected based on significant weight loss over lifestyle modification and modest improvements in weight-related co-morbidities. The effect of pharmacological weight-loss on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established.
- D. The expected duration of therapy is over a patient's lifetime.
- E. In addition to the most serious risks of medullary thyroid carcinoma and acute pancreatitis, SAXENDA (liraglutide) also has the following risks: acute gallbladder disease, heart rate increase, hypoglycemia when used with an insulin secretagogue (e.g., a sulfonylurea) or insulin, renal impairment, and hypersensitivity.
- F. SAXENDA (liraglutide) is a not a new molecular entity.

The REMS will consist of a communication plan and a timetable for submission of assessments of the REMS.

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<sup>1</sup> Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of Childhood and Adult Obesity in the United States, 2011-2011. *JAMA*. 2014; 311(8): 806-814.

<sup>2</sup> Hampp C, Kang EM, Borders-Hemphill V. Use of prescription antiobesity drugs in the United States. *Pharmacotherapy*. 2013; 33(12):1299-1307.

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/s/  
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JENNIFER R PIPPINS  
12/22/2014

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: December 11, 2014

Reviewer(s): Amarilys Vega, M.D., M.P.H, Medical Officer  
Division of Risk Management (DRISK)  
Kate Oswell, MA, Health Communications Analyst  
DRISK

Team Leader: Naomi Redd, Pharm.D, Acting Team Leader  
DRISK

Division Director: Cynthia LaCivita, Pharm.D, Acting Director  
DRISK

Subject: FDA's comments to Novo Nordisk regarding their proposed amendment (October 10, 2014) to the Saxenda REMS

Drug Name(s): Saxenda (liraglutide [rDNA] injection)

Therapeutic Class: Glucagon-like peptide -1 (GLP-1) receptor agonist

Dosage and Route: Solution for subcutaneous injection, prefilled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, 1.8 mg/ml, 2.4 mg/ml, 3 mg/ml (6 mg/ml 3 ml)

Application Type/Number: NDA 206321/Amendment

Submission Number: Seq. No. 0054

Applicant/sponsor: Novo Nordisk

OSE RCM #: 2014-77 and 2014-79

TSI #: TSI 894

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