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APPLICATION NUMBER:

22-341

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review - Addendum

Date	December 3, 2009
From	Hylton V. Joffe, M.D., M.M.Sc.
Subject	Cross-Discipline Team Leader Review - Addendum
NDA #	22-341
Applicant	Novo Nordisk
Date of Submission	May 23, 2008
PDUFA Goal Date	March 23, 2009
Proprietary Name / Established (USAN) names	Victoza (liraglutide)
Dosage forms / Strength	6 mg/mL formulation administered subcutaneously via 3 mL ——— as 0.6 mg, 1.2 mg, or 1.8 mg
Proposed Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Recommended:	*Approval, pending agreement on labeling.*

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This document is an addendum to the Cross Discipline Team Leader (CDTL) memorandum for Victoza (liraglutide). The purpose of this document is to summarize the following information that has become available after the CDTL memorandum was finalized.

1. A postmarketing case of liver failure in a liraglutide-treated patient
2. Two postmarketing cases of gastric perforation in liraglutide-treated patients
3. Updated calcitonin shift analyses, including follow-up information on the liraglutide-treated patient who had an increase in serum calcitonin to >50 ng/L as well as a postmarketing case of "suspected C-cell carcinoma"
4. Recommendations from the recently completed immunology consult describing the need for better characterization of immunogenicity in a postmarketing clinical trial

The information contained in this addendum does not alter my previous recommendation that liraglutide be approved.

1. Postmarketing case of liver failure

The sponsor submitted a safety report of liver failure regarding a 53-year old woman treated with liraglutide during an ongoing clinical trial. The patient was hospitalized with hepatic failure and encephalopathy after presenting with disorientation, visual hallucinations, aphasia, and asterixis approximately 3 years after starting treatment with liraglutide. She had mildly elevated serum alanine aminotransferase (ALT), alkaline phosphatase, and gamma glutamyl transferase (GGT) at screening and throughout the trial. Her ALT, alkaline phosphatase, and GGT values upon hospitalization were comparable to her screening and on-treatment values. Total bilirubin was 2.1 mg/dL (1.9x ULN). During the 3 years of liraglutide treatment, the patient's total bilirubin values were mostly within normal limits, although on 5 occasions, her total bilirubin exceeded the upper limit of normal (maximum value prior to hospitalization was 1.5x ULN at Week 92). The patient was treated with lactulose, improved within 72 hours and was discharged after a 9-day hospital stay. The cause for the liver failure is unknown – the patient did not have a history of alcohol abuse, was not taking any culprit medications, and tested negative for various causes of hepatitis, including hepatitis B and C, autoimmune hepatitis, alpha-1-antitrypsin, and Wilson's disease. Of note, the transferrin saturation was 56% suggesting hemochromatosis as a possible cause, although this condition was not further evaluated with genetic testing, there is no information on family history, and the patient was from Mexico (most cases of hemochromatosis occur in Caucasians). Liver biopsy confirmed cirrhosis but there is no mention of whether there was staining for iron. Liraglutide is not a likely explanation for the liver failure based on the fact that the patient had abnormal liver test measurements at screening that did not appreciably change during the treatment period. There is no signal for hepatotoxicity in the liraglutide new drug application, as discussed in the CDTL memorandum.

2. Postmarketing cases of gastric perforation

The sponsor submitted a 7-day safety report of a 52 year-old man in Germany who developed gastric perforation approximately two weeks after starting liraglutide. He was treated with laparatomy and oversewing of a gastric ulcer. The sponsor submitted another 7-day safety report of a 52 year-old man in Germany who developed gastric perforation and peritonitis approximately 1 week after starting liraglutide. The liraglutide dose at the time of both of these events was 1.2 mg. There are several similarities in the descriptions of these reports (same patient age, gender, country) and the sponsor is attempting to determine whether these 2 reports pertain to the same patient. One of these reports describes the presence of an ulcer, which may have predisposed the patient to gastric perforation. Liraglutide's effects on delaying gastric emptying could conceivably cause greater distension/pressure in the stomach, leading to perforation in susceptible individuals. However, such a conclusion would be premature based on limited information involving two (or possibly one) postmarketing cases. In addition, this has not been identified as a safety concern with the currently marketed glucagon-like peptide (GLP-1) agonist. The clinical reviewer for liraglutide should monitor for cases of gastric perforation post-approval via submitted 15-day Adverse Event Reporting System (AERS) cases and summary data in Periodic Update Safety Reports (PSURs).

3. Calcitonin data

The patient with an elevation in serum calcitonin to >50 ng/L:

In the CDTL memorandum, there is mention of one liraglutide-treated patient (and no comparator-treated patients) who developed a treatment-emergent elevation in serum calcitonin to >50 ng/L. As mentioned in the CDTL memorandum, this 48 year-old man was treated with liraglutide 1.8 mg as add-on to glimepiride and had serum calcitonin values of 10.7 ng/L at Week 0, 30.7 ng/L at Week 12 and 53.5 ng/L at Week 26. The patient did not report any thyroid-related adverse events. After finalization of the CDTL memorandum, we received updated information on this patient. He had a follow-up serum calcitonin of 22.3 ng/L obtained more than 2.5 years after the last dose of liraglutide with an estimated glomerular filtration rate of 56 mL/min suggesting mild renal impairment. The sponsor recommended that the patient be referred to an endocrinologist for further evaluation.

The largest increase in serum calcitonin in a comparator-treated patient was seen with glimepiride in a patient whose serum calcitonin increased from 19.3 ng/L at baseline to 44.8 ng/L at Week 65 and 38.1 ng/L at Week 104.

7-day report of "suspected C-cell carcinoma":

On November 26, 2009, the sponsor submitted a 7-day report of "suspected C-cell carcinoma" in a patient receiving liraglutide 1.8 mg and insulin Detemir in an ongoing clinical trial. This diagnosis is based solely on serum calcitonin values – the patient has not yet undergone

thyroidectomy. Of note, this patient had a baseline (pre-liraglutide) serum calcitonin of 15.8 pg/mL. Approximately 7 months later, while on liraglutide, the patient underwent pentagastrin stimulation testing. The peak serum calcitonin during this test was 128 pg/mL, prompting referral for thyroidectomy. However, the serum calcitonin was 16.1 pg/mL immediately prior to pentagastrin administration, which is similar to the baseline value of 15.8 pg/mL. Therefore, I agree with the sponsor's assessment that the condition causing the calcitonin elevation was present prior to initiation of liraglutide and that it is unlikely that the exposure to liraglutide played a causal role in the underlying thyroid abnormality.

Updated shift data for serum calcitonin:

Table 1 summarizes calcitonin shift data and is virtually identical to Table 15 included in the CDTL memorandum. The only difference between Table 1 here and Table 15 in the CDTL memorandum is the inclusion of data shown in the shaded rows. These data were requested for completeness after the CDTL memorandum was finalized. The previously available data show the rates for patients meeting various calcitonin shift criteria over selected time periods (e.g., first 20/24/26/28 weeks, first 52 weeks, 104 weeks) using last-observation-carried forward for missing data. The newly available data show the rates for patients meeting the calcitonin shift criteria at any point during their treatment with study medication.

The bolded numbers in Table 1 correspond to rates that are numerically higher for liraglutide compared to the corresponding rates for placebo and active comparators. The liraglutide 0.6 mg dose and the 1.2 mg dose were not more likely than comparators to meet the calcitonin shift criteria shown in Table 1. Each column in Table 1 contains 16 incidence rates and there are only 2/16 incidence rates for 0.6 mg and 1/16 incidence rates for 1.2 mg that are numerically higher for liraglutide compared to control. There are 10/16 incidence rates for 1.8 mg that are numerically higher for liraglutide compared to control. However, it is noteworthy that the patients with the longest exposure to liraglutide (e.g., Week 104 data) did not have higher rates of calcitonin shifts compared to control. Lastly, a majority of the incidence rates (9/16) for total liraglutide were numerically lower than the corresponding incidence rates for control.

The one liraglutide-treated patient with an increase in serum calcitonin to ≥50 ng/L is discussed above and the patients with an increase in serum calcitonin to ≥20 ng/L are discussed in the original CDTL memorandum. Note that the CDTL memorandum counts 11 patients with a serum calcitonin increase to ≥20 ng/L when in fact there were 12 such patients (the twelfth patient is the patient described above who had an increase to ≥50 ng/L). This is clarified in the text below:

A total of 11 liraglutide-treated patients (two with 0.6 mg, one with 1.2 mg, and eight with 1.8 mg), five active comparator-treated patients, and one placebo-treated patient developed at least one treatment-emergent serum calcitonin ≥20 ng/L and <50 ng/L. One additional liraglutide-treated patient had an increase in serum calcitonin to ≥50 ng/L and is discussed separately above. One of the 11 liraglutide-treated patients with an increase in serum calcitonin to ≥20 ng/L and <50 ng/L had an increase in serum calcitonin from 2.1 ng/L at baseline to 22.4 ng/L at Week 12. There are no additional calcitonin data because the patient was discontinued

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