CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-341

SUMMARY REVIEW

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Summary Basis for Regulatory Action

Date	January 25, 2010
From	Curtis J. Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	NDA 22-341
Applicant Name	NOVO Nordisk
Proprietary / Established (USAN) Names	Victoza Liraglutide (rDNA origin) Injection
Dosage Forms / Strength	Injectable solution (6mg/mL) 0.6 mg, 1.2 mg, and 1.8 mg
Proposed Indication(s)	Treatment of Type 2 Diabetes Mellitus
Action:	*Approval*

Introduction

This review will be a brief summary of the basis for the regulatory action regarding liraglutide. Please refer to the reviews in the action package for a more detailed discussion. Liraglutide is a glucagon-like peptide-1 (GLP-1) analogue. GLP-1 is an intestinal peptide released in response to food ingestion that has an enhancing effect on insulin secretion when serum glucose is elevated and also has an inhibitory effect on glucagon (thereby inhibiting hepatic glucose synthesis) as well as slowing gastric emptying. GLP-1 has minimal, if any, effect on insulin secretion when glucose is normal or low and therefore GLP-1 analogues, by themselves, have less hypoglycemia as compared to some of the other agents used to treat diabetes. Intrinsic GLP-1 is degraded in minutes by dipeptidyl peptidase IV (DPP-4) which limits its clinical use; however, the analogues have prolonged pharmacokinetic profiles which allow a practical dosing interval.

The Agency has recently approved one other GLP-1 analogue, Byetta (exenatide) which is administered twice-daily as a subcutaneous injection. In addition, several others are in various stages of development.

As an overview, the efficacy of this drug is not in question. However, there are preclinical and clinical safety concerns that have led to differing opinions among the reviewers within the division as to whether liraglutide should be approved for marketing.

Preclinical rodent studies demonstrated C-cell hyperplasia (considered a pre-neoplastic lesion for medullary thyroid cancer in rodents) and C-cell tumor findings in two different rodent species (both sexes) at clinically relevant doses. Deciding on a course of action in regard to this finding is new territory for the agency. As we have yet to encounter this, we have not determined what this finding may mean in regard to human use and the concern is that it may be an indication that use of this drug will place humans at risk for medullary thyroid cancer

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(MTC). MTC is a very rare tumor in humans, with about 600 cases a year. Therefore, the question in regard to this preclinical finding, while probably only applying to a very small population, is what is the strength of uncertainty and whether or not the clinical benefit/utility would justify marketing in the face of uncertainty. If we were to allow marketing, this then brings into question what type of monitoring would we consider (if any) for what is a very rare event in humans. It should also be noted that the decision made in this regard does not affect just liraglutide, as Dr. Bruno-Davis has noted that data under review from other GLP-1 receptor agonists with longer half-lives as well as sustained-release formulations of short-acting analogues suggest that they all have this effect in rodents and that it is probably related to persistent receptor activation. It is interesting to note that a sustained-release formulation for exenatide, also seems to exhibit this findings while the immediate-release form did not, although as I will discuss below, the preclinical studies for the immediate-release form did not reflect the frequent dosing interval used in humans.

While the pre-clinical findings are the main concern with this application, there are also cardiovascular and pancreatic clinical issues that need consideration.

Regarding cardiovascular issues, control of hyperglycemia by hypoglycemic drugs has consistently demonstrated benefits in microvascular outcomes (retinopathy, neuropathy, renal function) but not so for macrovascular events (stroke, myocardial infarct). This is not a new finding, as sulfonylurea drugs have carried labeling indicating that they may increase cardiovascular mortality up to 2.5 times that of patients treated with diet alone. However, in the last two to three years, there have been increasing concerns that other anti-diabetic drugs may also increase cardiovascular events. This has led to debate regarding the adequacy of cardiovascular risk assessment during development programs. This is important as cardiovascular disease is very common in the general population and patients with diabetes have an additional 2 to 4 times increase risk compared to matched non-diabetic populations. Therefore, from a population health standpoint, if a drug increases cardiovascular risks it would affect a very large number of patients. These issues were discussed at an Advisory Committee meeting in July of 2008, where the panel recommended that glycemic control agents for type 2 diabetes coming before the agency should at a minimum have some type of screening pre-approval cardiovascular assessment, with further, definitive, post-approval testing. After much internal deliberation and consideration of the recommendations we received from AC panel members, we issued a final guidance that incorporated recommendations from that meeting. This guidance, in accord with the recommendations we received, allows for two 'step-wise' assessments of potential cardiovascular risk during drug development. Step-one occurs during the development program before marketing, and requires making a determination that the investigational agent has an upper bound of a two-sided 95 percent confidence interval for the estimated risk ratio of less than/equal to 1.8 compared to a control group (with a point estimate near unity). This would assure that at a minimum, the drug does not double the risk of cardiovascular disease. Demonstration that less than a 1.8 increase exists allows marketing while a longer and larger outcome study is conducted. The concept is that any further or more definitive pre-approval testing would be too burdensome to drug development, but this level of definition described above would be feasible/practical and would provide some assurances while further testing was underway. Further testing would be accomplished by a larger outcome study that must demonstrate that

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the investigational agent has an upper bound of a two-sided 95 percent confidence interval for the estimated risk ratio of less than/equal to 1.3 (rule out a 30% increase, smallest amount of difference felt to be generally practical) compared to a control group in order for continued marketing to occur.

These principles incorporate recommendations from the advisory committee. The details of this approach are outlined in the guidance[1], but of relevance is that at the time of issuance of the guidance, three NDAs were in review. We concluded that recommendations should apply to all ongoing programs including those with applications pending with the agency at the time of guidance issuance. Although not totally in alignment with the guidance, liraglutide as well as saxagliptin seemed to, in spirit, fulfill 'step-one' and both were presented at a subsequent advisory committee meeting for discussion. The majority of the panel at that meeting voted that liraglutide (and saxagliptin) had fulfilled step-one requirements which would allow for marketing while awaiting the results of a definitive study.

Pancreatitis has been identified in post-marketing reporting with the use of incretin-based therapies. We have received reports for both exenatide (Byetta) and sitagliptin (Januvia-a dipeptidyl-peptidase IV inhibitor) and these reports also included cases of hemorrhagic/necrotizing pancreatitis. While the preclinical animal studies and pre-marketing clinical development program for exenatide and sitagliptin did not detect a signal, a recent publication[2] in a transgenic rat model that expresses human islet amyloid polypeptide (IAPP or amylin) did note that rats exposed to sitagliptin increased pancreatic ductal cell turnover, demonstrated metaplasia of these cells and one animal had pancreatitis (hemorrhagic). While further exploration of these findings is necessary, this does provide a possible mechanistic hypothesis for pancreatitis in regard to drugs that exert there effects through the incretin system. The published report referred to above along with the post-market reports gives us great concern and will lead us to have further studies in animal models that are a closer approximation to the disease state of Type 2 diabetes.

The preclinical evaluation for liraglutide did note increased pancreatic organ weight, but treatment-related microscopic pathology, overt pancreatitis or pancreatic cancer was not identified. Other studies conducted in a variety of animal models that give a closer approximation to Type 2 diabetes (insulin deficiency but not resistance as noted in Dr. Parks memo), did not reveal any serious gross pancreatic pathology although none of these models display the complete clinical presentation of diabetes and were not performed as toxicology studies so they did not include careful histopathology evaluations. However, there were several cases of pancreatitis in subjects during the liraglutide clinical development program, with a greater number associated with the use of liraglutide than controls, even after correcting for exposure. This adds to the body of evidence that is accumulating that incretin-based therapies may have some type of detrimental effect in the pancreas.

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[1] Diabetes Mellitus-Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, December 2008, Clinical/Medical.

[2] Matveyenko AV, Dry S, Cox HI, Beneficial endocrine but adverse exocrine effects of sitagliptin in the human islet amyloid polypeptide transgenic rat model of type 2 diabetes: interactions with metformin. Diabetes. 2009 Jul; 58(7):1604-15

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I will discuss these issues as well as provide an overview of the efficacy findings below.

Efficacy

This has been thoroughly discussed in Drs. Derr, Yanoff, Joffe and Parks reviews and I agree with their conclusions. The following table from Dr. Parks review (Page 17), summarizes the important randomized trials.

Table 7.1 Summary of Pivotal Phase 3 Studies

Study #	Treatment Groups	Background Therapy	Mean Baseline HbA1c	Mean Duration of Diabetes (yrs)
Monotherapy				
Study 1573	Lira 1.2 mg Lira 1.8 mg Glimepiride 8 mg	Diet and exercise	8.2	5.4
Add-on to Single OAD (Dual Therapy)				
Study 1572	Lira 0.6 mg + met 2g Lira 1.2 mg + met 2g Lira 1.8 mg + met 2g Metformin 2g Glimepiride 4mg + metformin 2g	Metformin	8.4	7.4
Study 1436	Lira 0.6 mg + glim 4mg Lira 1.2 mg + glim 4mg Lira 1.8 mg + glim 4mg Glimepiride 4 mg Rosiglitazone 4 mg + glim 4mg	Glimepiride	8.4	7.9
Add-on to Two OADs (Triple Therapy)				
Study 1574	Lira 1.2 mg + met 2g + rosi 8 mg Lira 1.8 mg + met 2g + rosi 8 mg Metformin 2g + rosi 8 mg	Metformin + rosiglitazone	8.5	9.0
Study 1697	Lira 1.8 mg + glim 4 mg + met 2g Glim 4 mg + met 2 g Insulin glargine + glim 4 mg + met 2g	Metformin + glimepiride	8.3	9.4

The primary endpoint was change from Baseline of HbA1c either after 52 weeks (Study 1573) or 26 weeks (remaining studies). The review team concluded that the 0.6 mg dose demonstrated minimal efficacy compared to the 1.2 mg and 1.8 mg doses. The following table from Dr. Joffe's review (Page 17) summarizes the findings from these trials.

Table 3. Change from baseline in HbA1c (%) (intent-to-treat population with last-observation-carried-forward)

	N	Baseline±SD	Adjusted mean change±SE	Change with lira relative to change with placebo		Change with lira relative to change with comparator	
				Mean difference (95% CI)	p-value	Mean difference (95% CI)	p-val
Monotherapy (Study 1573) – 52 weeks							

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