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APPLICATION NUMBER:

203313Orig1s000
203314Orig1s000

OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	September 25, 2015
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # **Supp #**	203314 203313
Applicant Name	Novo Nordisk Inc.
Proprietary / Established (USAN) Names	Tresiba (Insulin degludec) (203314) Ryzodeg (Insulin degludec/insulin aspart) (203313)
Dosage Forms / Strength	Solution for sc injection U100 and U200 (Tresiba) U100 (Ryzodeg)
Proposed Indication(s)	Improvement of glycemic control in adults with diabetes mellitus
Action:	*Approval*

1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding insulin degludec (i.e., Tresiba) and insulin degludec/aspart 70/30 fixed-ratio combination (i.e., Ryzodeg 70/30) products and the reader should review the action package and my review from the first cycle for more detail. Tresiba and Ryzodeg 70/30 are both insulin products that contain insulin degludec, a long-acting human insulin analog intended for once-daily use basal therapy in patients with type-1 and type-2 diabetes mellitus. Insulin aspart is a short-acting insulin analog. The dosage of both drugs is to be individualized based on glycemic response, with no upper dosage-limit. Insulin glargine (Lantus) and insulin detemir (Levemir) are two other long-acting insulin analog products currently approved in the United States intended for basal therapy.

Insulin therapy is life-saving in type-1 diabetes mellitus (T1DM) as patients are no longer able to produce their own insulin. Insulin therapy is also important in the management of type-2 diabetes (T2DM) as the disease progresses and patients become refractory to other non-insulin therapies. During the first cycle review of the above products, a concerning possible cardiovascular (CV) signal was demonstrated in a thorough, well-designed, prospectively planned meta-analysis of trials which included rigorous blinded adjudication. At that time, I determined that in order to justify allowing marketing and taking a risk that the CV effect may be real (while performing formal CV evaluations post-approval) there needs to be some counterbalancing benefits that degludec has above glargine to allow marketing, which was not demonstrated.

Therefore, I determined that:

"The sponsor will need to start a dedicated CVOT[1] in degludec and it should be compared to glargine, where we have some data indicating a neutral risk. I believe we could allow marketing with appropriate interim data. If they have neutral or better data at that time, I would allow marketing."

The efficacy of both of these products was evaluated during the first review cycle and will not be discussed again in this review. The safety was also thoroughly evaluated during the first review cycle and there were no unexpected findings except for the possible adverse cardiovascular effect. This CR response contains a safety update and interim results from a CVOT (DEVOTE). The interim results from DEVOTE are reassuring and the team is recommending approval of both applications. I agree with their recommendation.

Safety

Additional safety information was provided that increased the overall exposure by approximately 40% compared to the last review. This increase in exposure did not substantially change the conclusions from those of the initial review cycle. The other main consideration is the interim analysis from the CVOT.

Cardiovascular Safety

We informed the sponsor that we would require information from a dedicated CVOT that had a reassuring point estimate and excluded a risk margin of 1.8 in order to allow marketing. The interim data from DEVOTE fulfill these criteria. The study plans on continuation with the goal of ultimately ruling out an upper margin of 1.3.

Advisory Committee Meeting

There was not a repeat AC for the complete response. We did not have further questions for the committee that were not covered during the AC of November 8, 2012.

Conclusions and Recommendations

Tresiba and Ryzodeg 70/30 have efficacy in the treatment of T1DM and T2DM and can be used in such a fashion as to be non-inferior to other comparable, approved and marketed insulin products. The issue that led to a CR during the first cycle has been adequately evaluated and is resolved. This application can be approved with appropriate labeling.

[1] Cardiovascular outcomes trial

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/s/

CURTIS J ROSEBRAUGH
09/25/2015