FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) Meeting
FDA White Oak Campus, Building 31, The Great Room (Rm. 1503)
White Oak Conference Center, Silver Spring, Maryland
November 8, 2012

QUESTIONS TO THE COMMITTEE

1. **Cardiovascular Safety (Discussion):** As agreed with the FDA, the degludec and degludec/aspart programs were not designed to rule out a pre-specified margin of cardiovascular (CV) risk. However, at the End-of-Phase 2 meeting, FDA informed the applicant that this program was still required to collect and analyze CV data from clinical trials as outlined in the December 2008 Guidance for Industry. Based on the information provided in the briefing package and the presentations at today's meeting, please comment on the reliability of the CV risk assessment with respect to:

   a. The CV endpoints included in the primary analysis for CV risk

   b. The adjudication process in the CV meta-analysis

   c. The patient population included in the CV risk assessment

   d. The design of the clinical program (e.g., open-label nature) and the impact, if any, this may have had on reporting, collecting and interpreting the results of the CV meta-analysis

   e. The original meta-analysis of 16 clinical trials versus the updated meta-analysis of 17 clinical trials including the extension phases of 6 trials in the original meta-analysis

2. **Cardiovascular Safety (Discussion):** Based on your response to question 1, please discuss whether the CV safety signal identified in the degludec and degludec/aspart program represents a clinical concern in the management of Type 1 and Type 2 diabetes mellitus (DM). In your discussion, please consider the background CV risks of patients requiring insulin for the management of their diabetes.

3. **Hypoglycemia Risk Assessment (Discussion):** The applicant performed several pre-specified secondary analyses of hypoglycemia data across several trials in the degludec and degludec/aspart programs and a pre-planned meta-analysis to compare the risk of "confirmed hypoglycemic events" between insulin degludec and insulin glargine.

In these analyses "confirmed hypoglycemic episodes," represent the sum of "severe episodes" and "Novo Nordisk minor episodes."

QUESTIONS TO THE COMMITTEE (cont.)

- A severe episode was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

- A Novo Nordisk minor episode was defined as an episode not requiring third party assistance where a plasma glucose < 56 mg/dL or whole blood glucose <50 mg/dL was recorded (i.e., with or without presence of hypoglycemic symptoms).

Other definitions for hypoglycemia and their rates have been presented.

Based on the information provided in the briefing package and the presentations at today's meeting, please discuss the following:

a. The clinical relevance of the results of the pre-planned meta-analysis of hypoglycemia relying on the Novo Nordisk definition of "confirmed" hypoglycemic episodes. Please consider in your discussion the following:

    i. the differences in hypoglycemic risk between types of diabetes (Type 1 DM vs. Type 2 DM)

    ii. the differences in hypoglycemic risk between geographic regions (U.S. versus non-U.S.) observed in the meta-analysis of hypoglycemia

b. In the overall program, comment on the clinical relevance of the hypoglycemic event findings. Please consider in your discussion the following:

    i. Consistencies and/or inconsistencies of the findings

    ii. The time frame used to define the nocturnal time period and how pharmacodynamic differences and timing of injection of degludec versus comparators might inform these results

    iii. The hypoglycemic results in the context of glycemic efficacy of degludec relative to the comparators

QUESTIONS TO THE COMMITTEE (cont.)

4. **Pharmacokinetic Profile (Discussion):** Please comment on the long duration of action of degludec with respect to its dosing regimen and what clinical relevance this may have to patients with Type 1 or Type 2 DM.

5. **Vote:** Based on the results from the CV meta-analysis, should a cardiovascular outcomes trial be conducted for degludec and degludec/aspart?

   a. If you voted "Yes" to question #5, please provide your rationale

   b. If you voted "No" to question #5, please provide your rationale

6. **Vote:** Based on the information included in the briefing materials and presentations today, has the applicant provided sufficient efficacy and safety data to support marketing of degludec and degludec/aspart for the treatment of Type 1 and Type 2 diabetes mellitus?

   a. If you voted "Yes" to question #6, please provide your rationale and whether you recommend any additional studies post-approval.

   b. If you voted "No" to question #6, please provide your rationale and discuss what additional data are necessary to potentially support approval.