

**Food and Drug Administration
Center for Drug Evaluation and Research**

**Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee
Meeting
November 8, 2012**

Location: FDA White Oak Campus, Building 31, the Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland.

Topic: The committee discussed the safety and efficacy of new drug applications (NDA) 203313, insulin degludec/insulin aspart [rDNA origin] injection and (NDA) 203314, insulin degludec [rDNA origin] injection, manufactured by Novo Nordisk Incorporated. The proposed indication (use) for these applications is for the treatment of Type 1 and Type 2 diabetes mellitus.

These summary minutes for the November 8, 2012 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration were approved on January 30, 2013.

I certify that I attended the November 8, 2012 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

-Signed-

Paul T. Tran, RPh
Designated Federal Officer, EMDAC

-Signed-

Kenneth Burman, MD
Acting Chairperson, EMDAC

**Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee
Meeting
November 8, 2012**

The following is the final report of the Endocrinologic and Metabolic Drugs Advisory Committee meeting held on November 8, 2012. A verbatim transcript will be available in approximately six weeks, sent to the Division of Metabolism and Endocrinology Products and posted on the Food and Drug Administration (FDA) website at:

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/default.htm>

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Endocrinologic and Metabolic Drugs Advisory Committee of the FDA, Center for Drug Evaluation and Research, met on November 8, 2012 at the FDA White Oak Campus, Building 31, The Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Novo Nordisk, Inc. The meeting was called to order by Kenneth Burman, MD (Acting Chairperson), and the conflict of interest statement was read into the record by Paul Tran, RPh (Designated Federal Officer). There were approximately 150 people in attendance. There were eleven Open Public Hearing speakers.

Issue: The committee discussed the safety and efficacy of new drug applications (NDA) 203313, insulin degludec/insulin aspart [rDNA origin] injection and (NDA) 203314, insulin degludec [rDNA origin] injection, manufactured by Novo Nordisk Incorporated. The proposed indication (use) for these applications is for the treatment of Type 1 and Type 2 diabetes mellitus.

Attendance:

Endocrinologic and Metabolic Drugs Advisory Committee Members Present (Voting):
Erica H. Brittain, PhD; Ed J. Hendricks, MD; Ellen W. Seely, MD (*via telephone*); Robert J. Smith, MD

Endocrinologic and Metabolic Drugs Advisory Committee Members Not Present (Voting):
Vera Bittner, MD, MSPH; David M. Capuzzi, MD, PhD; Edward W. Gregg, PhD; Ida L. Spruill, PhD, RN (*Consumer Representative*)

Acting Industry Representative to the Committee (Non-Voting):
Rob Scott, M.D. (*Acting Industry Representative*)

Temporary Members Present (Voting):
Kenneth D. Burman, MD (*Acting Chairperson*); David W. Cooke, MD; Brendan M. Everett, MD, MPH; William R. Hiatt, MD, FACP; Rebecca W. Killion (*Patient Representative*); Marvin A. Konstam, MD; Charles A. Stanley, MD; Thomas J. Weber, MD

FDA Participants (Non-Voting):

Jean-Marc Guettier, MDCM; Mary H. Parks, MD; Curtis J. Rosebraugh, MD, MPH; Mat Soukop, PhD

Designated Federal Officer: Paul T. Tran, RPh

Open Public Hearing (OPH) Speakers: Jean Jones; Thomas W. Donner, MD (American Diabetes Association); Charles Shaefer, MD; George Grunberger, MD, FACP, FACE (American Association of Clinical Endocrinologists); Christopher H. Sorli, MD, PhD; Bennet Dunlap, MSHC; Erin Cutrell (statement read by Laura Dunn); Laura Ely Dunn; Kelly L. Close (diaTribe); Jeannette Crim; Riccardo Perfetti, MD, PhD (Sanofi)

The agenda proceeded as follows:

Call to Order and Introduction of Committee	Kenneth D. Burman, MD Acting Chairperson, EMDAC
Conflict of Interest Statement	Paul T. Tran, RPh Designated Federal Officer, EMDAC
Introduction/Background	Jean-Marc Guettier, MDCM Diabetes Team Leader Division of Metabolism and Endocrinology Products (DMEP) Office of Drug Evaluation II (ODE-II) Office of New Drugs (OND), CDER, FDA
SPONSOR PRESENTATIONS	Novo Nordisk, Inc.
Introduction	Robert Clark Vice President Regulatory Affairs Novo Nordisk
Defining the Rationale for an Improved Insulin	Bernard Zinman, CM, MD, FRCPC, FACP Director, Leadership Sinai Centre for Diabetes Professor of Medicine, University of Toronto
Design of Insulin Degludec	Peter Kurtzhals, PhD Senior Vice President Diabetes Research Unit Novo Nordisk
Clinical Development Program, Efficacy and General Safety of IDeg and IDegAsp	Alan Moses, MD Global Chief Medical Officer Novo Nordisk

SPONSOR PRESENTATIONS (CONT.)

Cardiovascular Safety IDeg and IDegAsp **Anne Phillips, MD**
Corporate Vice President
Clinical Development, Medical and Regulatory Affairs,
Novo Nordisk

Assessing Cardiovascular Risk with Insulin
Degludec **Steve Marso, MD, FACC, FAHA, FSCAI**
Professor of Medicine
University of Missouri, Kansas City
Consulting Cardiologist
St. Luke's Cardiovascular Consultants

IDeg and IDegAsp Benefit/Risk Discussion **Anne Phillips, MD**

Clarifying Questions from the Committee

BREAK

FDA PRESENTATIONS

Clinical Safety **Karim Anton Calis, PharmD, MPH**
Clinical Reviewer
DMEP, ODE-II, OND, CDER, FDA

Cardiovascular Meta-Analysis **Bo Li, PhD**
Statistical Reviewer
Division of Biometrics VII (DB7)
Office of Biostatistics (OB)
Office of Translational Sciences (OTS), CDER, FDA

Hypoglycemia Meta-Analysis **Eugenio Andraca-Carrera, PhD**
Statistical Reviewer
DB7, OB, OTS, CDER, FDA

Clinical Perspective of Hypoglycemic
Analyses and Results **Jean-Marc Guettier, MDCM**

Clarifying Questions from the Committee

Lunch

Open Public Hearing Session

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Advisory 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

Committee Discussion: *The committee reviewed questions #1a, #1b, #1c and #1d together during one discussion. The committee agreed that this was not a primary cardiovascular study and there was general consensus from the committee that the CV endpoints included in the primary analysis for CV risk, which included major adverse cardiovascular events (MACE) and MACE+, were appropriate and reasonable. The adjudication process in the CV meta-analysis was performed by an independent group, looking objectively at these studies and the committee agreed that the adjudicating process was performed appropriately. The committee noted that the patient population included in the CV risk assessment was well-represented with regard to age and gender; however, it was also noted that there were a few ethnic groups under-represented in the studies. The committee commented that the open-label design of the clinical program could not be avoided and that the applicant did the best that they could to ensure that it would not have any impact on reporting, collecting and interpreting the results of the CV meta-analysis. Please see the transcript for details of the committee's discussion.*

- 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

Committee Discussion: *There was general consensus from the committee that the original meta-analysis of 16 clinical trials and the data from the updated meta-analysis of 17 clinical trials should be included in further analysis, although the data from the original analysis presents limitations with regard to the number of patients and number of events. The committee cautioned that the results are not definitive and further studies need to be conducted because of the limited data on cardiovascular (CV) events recorded in the study (since the study was not designed to capture CV endpoints) and the lack of understanding regarding C-reactive protein (CRP) and other cardiac endpoints such as*

cardiac echo and carotid sonogram. Please see the transcript for details of the committee's discussion.

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.

Committee Discussion: *The committee agreed that there was an increase in CV risk observed in most of the clinical trials and although some of the results were not statistically significant, they are potentially concerning. The committee recommended that further data could be captured with studies of patients with more advanced cardiovascular disease. The committee noted that MACE should be used but strict cardiac endpoints should be implemented in a longer term trial. Please see the transcript for details of the committee's discussion.*

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.”

- 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

Committee Discussion: *The committee reviewed the two subparts of question #3a during one discussion. The committee noted that the risk of hypoglycemia with the two agents between type 1 diabetes and type 2 diabetes are neither increased or decreased compared to the comparative agents in the studies; however, it was noted that type 1 diabetics are more prone to hypoglycemia episodes in general. The committee agreed that the Novo Nordisk definition of “confirmed” hypoglycemia, which was used in the studies, seemed appropriate but noted that the American Diabetes Association’s (ADA) definition would have been more optimal. Regarding the differences in hypoglycemia risk between geographical regions, the committee indicated that there were some differences seen between the U.S. versus the non-US sites but it was not statistically significant; however, they emphasized that further studies would be needed to confirm these findings. Please see the transcript for details of the committee’s discussion.*

- 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

Committee Discussion: *The committee reviewed the three subparts of question #3b during one discussion. The committee noted some inconsistencies in the hypoglycemic event findings; however, the committee expressed less of a concern over the inconsistencies because of the large number of patients enrolled in these studies and the number of exposure years. The committee recommended that the time frame for nocturnal period should be between 10 pm or midnight to 6 am, although extending this time frame until 8 am would also be appropriate. The committee also recommended that measurements are taken to capture not only HbA1c but also fasting glucose. The committee cautioned that because some of these studies excluded higher risk patients and thus may have underestimated the risks for daytime or nighttime hypoglycemia, further studies are needed. The committee noted the balance between glycemic efficacy versus glycemic risk relative to the comparators seemed appropriate and was less concerning to the committee overall. Again, the committee would like to have more data on the higher risk patient population. Please see the transcript for details of the committee’s discussion.*

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.

Committee Discussion: *The committee noted the unique pharmacokinetic profile of these two new agents with the half-life of 24 to 25 hours. It was also noted that another advantage of insulin degludec is the ability for it to be mixed with insulin aspart. The committee recommended further studies on the sites of injection to determine if there are differences in dissolution of the drug at the different sites of injection, such as the arm, abdomen or leg. The committee also noted that further studies are needed to better define the missed dose time frame and when the next dose can be safely administered. Please see the transcript for details of the committee's discussion.*

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

Yes: 12 No: 0

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

Committee Discussion: *The committee unanimously voted "Yes" to require a cardiovascular outcomes trial since there are potential signals for CV risk and a CV trial would need to be conducted to confirm. Please see the transcript for details of the committee's discussion.*

- 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?

Yes: 8 No: 4

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

Committee Discussion: *The committee members who voted "Yes" reiterated the need for a properly powered and well-designed study to assess the CV risk post-approval and the applicant's commitment to conduct such a CV trial was reassuring. Some members also suggested building specific milestones into the trials to capture early signals and to allow appropriate action to be taken if needed. Other members recommended specific endpoints in the post-approval trials such as lipids, CRP, cardiac echo and carotid Doppler studies. Please see the transcript for details of the committee's discussion.*

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

November 8, 2012

Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee

Committee Discussion: *The committee members who voted “No” noted the difficulty in reaching a decision concerning their vote and indicated they have concerns regarding the potential CV signals seen in the studies. Several members indicated that although insulin degludec and insulin degludec/aspart offer several advantages, the potential risk did not outweigh the benefit given there are other alternatives already available on the market. Several members agreed that the issue of hypoglycemia should be studied further. Please see the transcript for details of the committee’s discussion.*

The meeting was adjourned at approximately 4:20 p.m.