Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting
May 24, 2016

Location: The FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland.

Topic: The committee discussed the safety and efficacy of new drug application (NDA) 208583 for insulin degludec and liraglutide injection, submitted by Novo Nordisk Inc., for the proposed indication: adjunct to diet and exercise to improve glycemic control in the treatment of adults with type 2 diabetes mellitus.

These summary minutes for the May 24, 2016, meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration were approved on August 4, 2016.

I certify that I attended the May 24, 2016, meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
LaToya Bonner, PharmD
Designated Federal Officer, EMDAC

/s/
Robert J. Smith, MD
Chairperson, EMDAC

Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting
May 24, 2016

The following is the final report of the Endocrinologic and Metabolic Drugs Advisory Committee meeting held on May 24, 2016. A verbatim transcript will be available in approximately six weeks, sent to the Division of Metabolism and Endocrinology Products and posted on the FDA website at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm491062.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 (EMDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on May 24, 2016, at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, 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 Robert J. Smith, MD (Chairperson). The conflict of interest statement was read into the record by LaToya Bonner, PharmD (Designated Federal Officer). There were approximately 200 people in attendance. There were 13 Open Public Hearing (OPH) speaker presentations.

Issue: The committee discussed the safety and efficacy of new drug application (NDA) 208583 for insulin degludec and liraglutide injection, submitted by Novo Nordisk Inc., for the proposed indication: adjunct to diet and exercise to improve glycemic control in the treatment of adults with type 2 diabetes mellitus.

Attendance:

EMDAC Members Present (Voting): Daniel Budnitz, MD, MPH; Brendan M. Everett, MD, MPH; David W. Cooke, MD; Diana Hallare, MPH (Consumer Representative); James D. Neaton, PhD; (via telephone); Robert J. Smith, MD (Chairperson); Charles A. Stanley, MD; Peter W.F. Wilson, MD; Susan Yanovski, MD

EMDAC Members Not Present (Voting): Susan R. Heckbert, MD, PhD; William R. Hiatt, MD, FACP, FAHA

EMDAC Member Present (Non-Voting): Reshma Kewalramani, MD

Temporary Members (Voting): Kenneth Burman, MD; Marie C. Gelato, MD, PhD; Michael Reed, PharmD, FCCP, FCP; Timothy Lesar, PharmD; Steven B. Meisel, PharmD; Barbara Berney (Patient Representative); Martha Nason, PhD

FDA Participants (Non-Voting): Mary Parks, MD; Jean-Marc Guettier, MDCM; Lisa Yanoff, MD; Tania Condarco, MD; Anna Kettermann, Dipl. Math, MA

Designated Federal Officer (Non-Voting): LaToya Bonner, PharmD

Open Public Hearing Speakers: Kelly L Close (The diatribe Foundation); Christopher Tasik; Stanley Schwartz, MD (American Association of Clinical Endocrinologists); Lizmari M. Collazo; Paul Norwood, MD, FACP; Nicole Johnson, DrPH, MPH, MA; Nicole Kofman on behalf of Joyce Gresko; Steven Edelman, MD (Taking Control of Your Diabetes); Brian Cohen; Ava Runge (dQ&A); Emily Regier (Close Concerns); Douglas Herring; Robert Ratner, MD (American Diabetes Association)

The agenda was as follows:

Call to Order and Introduction of Committee	**Robert J. Smith, MD** Chairperson, EMDAC
Conflict of Interest Statement	**LaToya Bonner, PharmD** Designated Federal Officer, EMDAC
FDA Introductory Remarks	**Jean-Marc Guettier, MDCM** Director Division of Metabolism and Endocrinology Products (DMEP) Office of Drug Evaluation II (ODE-II) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Novo Nordisk, Inc.**
Introduction	**Robert Clark** Vice President, Regulatory Affairs Novo Nordisk
Rationale for the New Treatment Strategy	**Christopher Sorli, MD** Department Chair of Diabetes, Endocrinology and Metabolism Billings Clinic
Efficacy	**Stephen Gough, MD** Senior Principal Clinical Scientist Novo Nordisk
Safety	**Todd Hobbs, MD** Chief Medical Officer Novo Nordisk
Clarifying Questions to Applicant	

BREAK

FDA PRESENTATIONS

Clinical and Statistical Overview	**Tania Condarco, MD** Clinical Reviewer DMEP, ODE-II, OND, CDER, FDA **Anna Kettermann, Dipl. Math, MA** Mathematical Statistician Division of Biometrics II (DB-II) Office of Biostatistics (OB) Office of Translational Sciences (OTS), CDER, FDA
Human Factors Evaluation	**Ariane Conrad, PharmD, BCACP, CDE, FASCP** Safety Evaluator Division of Medication Error Prevention and Analysis Office of Medication Error Prevention and Risk Management (OMEPRM) Office of Surveillance and Epidemiology (OSE) CDER, FDA

Clarifying Questions to FDA

LUNCH

Open Public Hearing

Charge to the Committee

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss the benefit(s) of starting the fixed-combination drug product containing liraglutide and insulin degludec in patients with type 2 diabetes mellitus not treated with either a basal insulin or a GLP-1 agonist (i.e., starting two new drugs at once). In your discussion, identify the patient population in whom this use would be useful and address why you would select the fixed-combination product over use of an available GLP-1 agonist or basal insulin in these patients. Explain your rationale using data from the briefing materials and presentations, or from your own clinical experience.

Committee Discussion: *The committee agreed that insulin degludec and liraglutide (IDegLira) as a fixed ratio injection may provide a useful additional option for prescribers to manage adult patients with type 2 diabetes mellitus. However, the committee expressed difficulties in identifying a targeted population for IDegLira. Some members noted that a population that could benefit would be patients that would require insulin and in whom two agents would typically be introduced. Also, the committee noted that perhaps this therapy would not be considered on a patient that could be controlled on a GLP-1 alone. The committee proposed that the population who would benefit from starting two new drugs at once may be identified by their hemoglobin A1c:*

- *If HbA1c <7%, then starting one drug may be preferred*
- *If HbA1c of 7-9%, may be an appropriate population for use of IDegLira*

Some committee members indicated that the inclusion criteria of HgbA1c of 7-10% (in the clinical trials) could serve as a guide as to who could be treated with IDegLira.

Additionally, a few members proposed that patients who are reluctant to use insulin because of concern of side effects, such as weight gain, may be a population that could benefit from this combination.

Generally, the committee agreed that one injection per day may improve patient compliance compared to multiple injections per day. However, the committee indicated that initiating a treatment regimen of two separate classes of drugs at one time instead of the add-on sequential approach raised some concerns related to the risk of possible adverse events for patients who could achieve control with one drug, instead of two drugs. Further, a number of committee members questioned the efficacy of the dosing increments due to the capped dose of degludec. There was also concern regarding the efficacy of the liraglutide component at a dose below 1.2 mg. Please see the transcript for details of the committee discussion.

2. **DISCUSSION:** Discuss the benefit(s) of using the combination product containing liraglutide and degludec in patients with type 2 diabetes previously treated with either a basal insulin or a GLP-1 agonist (i.e., adding a single new drug to an existing regimen). In your answer, identify the patient population in whom use of the combination product in this manner would be useful. Explain your rationale using data from the briefing materials and presentations, or from your own clinical experience.

Committee Discussion*: The committee recognized that IDegLira may offer a new treatment option to an underserved population within the diabetic community, but struggled to reach a consensus on what sub-group of patients would be best served by the product. The committee expressed concern about efficacy in certain sub-group populations, such as obese patients who may have higher insulin requirements. The committee noted that it would be more acceptable to start IDegLira on a population that was either previous GLP-1 or previous insulin users. The committee noted the factors that would support the use of IDegLira include: aversion of two injections vs. one injection, patient's fear of weight gain from insulin, and cost savings from paying a co-pay for one medication vs. two medications.*

Some members stated that ease of titration could also make it easier for IDegLira to be used by primary care physicians, who may hesitate to start insulin due lack of comfort with insulin titration.

In regards to limitations of the data, the committee noted the following:

- *There is no clinical data for patients above 50 units of basal insulin.*
- *There is little data as to what happens to blood glucose control when the insulin dose is decreased in patients who are transitioned from insulin to IDegLira. There is no glycemic data to explain what happens to glycemic control, at the time of drug conversion.*

Please see the transcript for details of the committee discussion.

3. **DISCUSSION:** Discuss clinical concerns related to the use of the fixed-combination product which combines a drug that, when used alone, has a wide effective dose range and is titrated to effect on a continuous scale (i.e., insulin degludec) with a drug that, when used alone, has one or two recommended effective dose(s) (i.e., liraglutide).

   Specifically discuss:

   a. Issues related to loss of dosing flexibility including but not limited to: Use of potentially ineffective doses of one agent in populations with low insulin requirements, inability to dose the two drugs independently with the device presentation proposed, inability to increase the insulin dose beyond 50 units.

      Committee Discussion: *The committee noted concerns with the insulin dose limited to "50" as there are individuals, such as those with a high body mass index (BMI) who are likely to exceed this dose.*

      In general, the committee did not have substantial concern regarding safety issues. The committee noted that the safety data did not suggest additional safety issues that would not be anticipated from the individual drugs, when used in the combination. Overall, the committee members noted that side effects appeared dose dependent, thus the lower doses of the individual components, achieved by use of the combination, decreased the presence of adverse reactions in the combination product.

      There was some disagreement regarding lower doses of IDegLira and the efficacy of the liraglutide component. Some members noted that the data from the IDegLira phase 3 trials and from the phase 2 trial of liraglutide provided some comfort that low doses of IDegLira have some glucose lowering effect, maybe not enough as an independent agent, but some effect nonetheless. Other members stated that the data was not sufficient to suggest efficacy at low liraglutide doses. Please see the transcript for details of the committee discussion.

   b. Issues related specifically to product presentation/device including but not limited to: use errors that may occur in the care setting related to a lack of clarity on the amount of each

product delivered with each given dose, insufficient understanding that, unlike insulin products, the maximum dose for the combination is capped.

Committee Discussion: *The committee expressed concern regarding the potential risk of confusion for patients and physicians from the pen presentation which currently does not have any unit of measure. The committee noted that it was important to emphasize that this product contains two drug products, i.e. not just insulin. The committee stated that this point should be made clear to minimize potential medication errors from physicians who could potentially prescribe another drug with the same component of IDegLira (for example, Saxenda). Another concern of the committee was the possibility of a patient administering a second injection beyond 50, when the patient assumes this product is just insulin.*

Another issue noted by the committee regarding the pen included questions regarding the pen's starting dose. The committee asked if there was a thought of starting the pen at "10" rather than at "1" so that doses that were very low (and presumably not efficacious) would not be possible to administer.

The committee also addressed the issue of a unit-less pen and noted that there is the potential for confusion from a pen containing two drug products and not having units. Also, the committee was concerned that electronic medical record systems may not allow for a prescriber to order a dose without units.

The committee also discussed the maximal dose of the IDegLira pen and noted that the "dose cap" would influence who to start this product. The committee indicated that knowing about the dose cap of 50, would allow providers to decide for whom this product should be prescribed.

Generally, the committee agreed that labeling should be the primary strategy to inform users that IDegLira has two separate components in the device. Please see the transcript for details of the committee discussion.

4. **VOTE:** Based on data in the briefing materials and presentations at today's meeting, do you recommend approval of the liraglutide/degludec fixed-combination drug, delivered using the proposed device, for the treatment of adult patients with type-2 diabetes mellitus?

   Vote Result: Yes: 16 No: 0 Abstain: 0

   a. If you voted yes, explain your rationale and discuss whether use of the combination should be approved for patients who have never been treated with a basal insulin product or a GLP-1 product, for patients who are inadequately controlled on either a basal insulin product or a GLP-1 product or for both populations. Recommend additional post-approval studies if you think these are needed.

   b. If you voted no, explain your rationale and recommend additional pre-approval studies if you think these are needed.

Committee Discussion*: The committee unanimously voted "Yes", recommending the approval of the liraglutide/degludec fixed-combination drug, delivered using the proposed device, for the treatment of adult patients with type-2 diabetes mellitus. The committee members stated that IDegLira had met the pre-specified objectives for efficacy. The committee noted that IDegLira could potentially serve a medical need in some patients with type 2 diabetes but did not clearly delineate who that patient population was. The committee recognized that the products carried two sets of side effects but stated that the results appeared to suggest that the combination was associated with numerically fewer gastrointestinal effects compared to liraglutide alone (but more than insulin) and numerically less weight gain compared to insulin alone (but more than liraglutide). Members also indicated that IDegLira could potentially aid the patient population who could benefit from the dose range offered by the product by reducing injection burden. Some committee members also mentioned lower cost to patients in their decision (though no data addressing any issue of cost were presented or discussed at this advisory committee). Some members stated that this product could also potentially help overcome the fear of starting insulin and thus potentially help patients receive insulin earlier than they would otherwise. Nevertheless, the committee urged for the development of better guidelines prior to the marketing of the product to assist in identifying the appropriate patient population for this drug product.*

Please see the transcript for details of the committee discussion.

The meeting was adjourned at approximately 4:45 p.m.