

**Summary Minutes of the Endocrinologic and Metabolic
Drugs Advisory Committee Meeting
May 25, 2016**

The following is the final report of the Endocrinologic and Metabolic Drugs Advisory Committee meeting held on May 25, 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 25, 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 Sanofi Aventis c/o Sanofi U.S. Services, 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 120 people in attendance. There were eleven Open Public Hearing (OPH) speaker presentations.

Issue: The committee discussed the safety and efficacy of new drug applications (NDAs) 208673 for insulin glargine and lixisenatide injection, a fixed ratio drug product consisting of insulin and a GLP-1 receptor agonist, and 208471 for lixisenatide injection, a GLP-1 receptor agonist, submitted by Sanofi Aventis c/o Sanofi U.S. Services Inc., proposed for the treatment of adults with type 2 diabetes mellitus.

Attendance:

EMDAC Members Present (Voting): Daniel Budnitz, MD, MPH; Brendan M. Everett, MD, MPH; 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; David W. Cooke, MD;

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

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

FDA Participants (Non-Voting): Mary Parks, MD; Jean-Marc Guettier, MDCM; William Chong, MD; Suchitra Balakrishnan, MD; Lubna Merchant, PharmD

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

Open Public Hearing Speakers: Gloria Cunningham; Virginia Valentine; Stanley Schwartz, MD (American Association of Clinical Endocrinologists); Lizmari M. Collazo; Glen Sussman (ICCT Research International, Inc.); Maria Parrino; Kelly L. Close (The diaTribe Foundation); Robert Ratner, MD (American Diabetes Association); Emily Regier (Close Concerns); Hele Gao (dQ&A); David Garcia

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	Sanofi Aventis c/o Sanofi U.S. Services, Inc.
Introduction	Paul Chew, MD Senior VP Research and Development Sanofi
Need for Treatment Options	Neil Skolnik, MD Temple University School of Medicine
MoA Lixisenatide and iGlarLixi	John Newton, PhD VP Pharmacokinetics, Dynamics Sanofi
Efficacy of Lixisenatide and iGlarLixi	Rachele Berria, MD, PhD VP Head Diabetes Medical Unit Sanofi
Safety of Lixisenatide and iGlarLixi	Kristen Sharma, MD VP Global Diabetes and CV Pharmacovigilance Unit Sanofi

APPLICANT PRESENTATIONS (CONT.)

Contribution and Component Titration and Dose Capping **Rene Belder, MD**
Global Project Head
Sanofi

Benefit Risk **Luigi Meneghini, MD**
University of Texas Southwestern Medical Center

Clarifying Questions to Applicant

BREAK

FDA PRESENTATIONS

LIXISENATIDE

Introduction and Regulatory History
Summary of Efficacy and Safety **Suchitra Balakrishnan, MD, PhD**
Clinical Reviewer
DMEP, ODE-II, OND, CDER, FDA

Cardiovascular Outcome Trial (ELIXA)
Results **Yueqin Zhao, PhD**
Mathematical Statistician
Division of Biometrics VII (DB-VII)
Office of Biostatistics (OB)
Office of Translational Sciences (OTS), CDER, FDA

**LIXISENATIDE/INSULIN GLARGINE FIXED
RATIO COMBINATION (IGLARLIXI)**

Introduction to the Combination Product **Suchitra Balakrishnan, MD, PhD**

Efficacy of the Combination Product **Jiwei He, PhD**
Mathematical Statistician
Division of Biometrics II (DB-II)
OB, OTS, CDER, FDA

Secondary Endpoints, Safety
Generalizability, and Clinical Considerations **Suchitra Balakrishnan, MD, PhD**

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

Summary **Suchitra Balakrishnan, MD, PhD**

Clarifying Questions to FDA

LUNCH

Open Public Hearing

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss any issues related to the efficacy or safety of lixisenatide for the treatment of patients with type 2 diabetes mellitus. Please comment on whether any of these issues preclude approval of lixisenatide.

Committee Discussion: The committee agreed that the data shown demonstrated the efficacy of lixisenatide and that it's comparable to other products in the same drug class. However, the committee noted concerns of the occurrence of unpredictable severe allergic reactions, and proposed ongoing monitoring for severe allergic reactions if the product is approved. The committee did not find any safety concerns that would preclude the approval of lixisenatide. Please see the transcript for details of the committee discussion.

2. **DISCUSSION:** Discuss the benefit(s) of starting the fixed-combination drug product containing lixisenatide and insulin glargine 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 particularly useful, and address why you would select the fixed-combination over use of an available GLP-1 agonist or basal insulin in these patients. Explain your rationale using data from the briefing materials, presentations, or your own clinical experience.

Committee Discussion: The committee acknowledged that the fixed-combination drug product addresses a need for additional therapies within the diabetic community, but struggled to reach a consensus on what sub-group of patients would be better served by the combination injection. While a firm consensus wasn't obtained, some members suggested that this fixed-ratio product might be of use in certain insulin naïve patients, but did not clearly identify this patient sub-group. The committee also expressed hesitancy to start treatment with two medications at once due to the concerns of administering unnecessary treatment and exposing patients to a higher risk of avoidable adverse events. The practitioners on the committee noted that they'd rather treat their patients sequentially to gain a sense of which medication is yielding an advantageous or ineffective outcome. Please see the transcript for details of the committee discussion.

3. **DISCUSSION:** Discuss the benefit(s) of using the fixed-combination drug product containing lixisenatide and insulin glargine 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 fixed-combination drug product in this manner would be particularly useful. Explain your rationale using data from the briefing materials, presentations, or your own clinical experience.

Committee Discussion: *Generally, the committee expressed their concerns with using two separate class of drugs simultaneously in managing adults with type 2 diabetes mellitus. Most commented on the risks of exposing patients to preventable side effects while others expressed the uncertainty of not knowing which agent is effective. The committee members all agreed that the limited data shown demonstrate the effectiveness of the fixed combination. The committee also noted that there was no data presented on patients who were already on a GLP-1 agonist so the applicant should conduct a study to address this. The committee acknowledged that the data shown indicated less weight gain in individuals administered the combination product compared to the use of basal insulin alone. Therefore, the committee recognized that this product may be effective in some adults with type 2 diabetes who failed to reach their therapeutic goal (A1C of 7%) with insulin. Please see the transcript for details of the committee discussion.*

4. **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 glargine) with a drug that, when used alone, has one or two recommended effective dose(s) (i.e., lixisenatide).

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 60 units.

Committee Discussion: *The committee was not too concerned about the loss of dosing flexibility with the fixed-combination product. The committee was also not concerned with the lower than effective dose of the GLP-1 agonist and the 60 unit capped insulin dose provided by the pen. It was noted that in practice most providers will re-strategize their approach by adding or substituting with another agent if patients needed more than 60 units of insulin. Please see the transcript for details of the committee discussion.*

- b. Issues related specifically to product presentation/devices 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, inadequate understanding of the role of the two devices.

Committee Discussion: *The committee agreed that the devices should be labeled in such a way that there is adequate understanding of the components of the fixed combination product particularly during transitions in care. The committee acknowledged the applicant's efforts to provide patients with dose flexibility by incorporating two separate pens. The committee noted that the term of measurement for administration is in "units", which heightens the concern that patients will mistakenly conclude that the fixed combination product is an insulin product. Thus, the committee advocated for a method to denote the terms of measurement such that it is clear that the product is not insulin and that it contains two drug substances prior to approval. Overall, the committee agreed that appropriately labeling the devices could assure that users are aware of the two drug substances, recognize the differences of dose in the two different pen injectors, and reduce the probability of prescribing errors. Please see the transcript for details of the committee discussion.*

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

Vote Result: Yes: 12 No: 2 Abstain: 0 No Voting: 1

- a. If you voted yes, explain your rationale and discuss whether use of the combination should be approved for patients not treated with a basal insulin or a GLP-1, for patients who are inadequately controlled on either a basal insulin or a GLP-1 analog or for both populations. Recommend additional post-approval studies if you think these are needed.

Committee Discussion: *The majority of the committee voted "Yes", recommending the approval of the lixisenatide/glargine fixed-combination drug delivered using the proposed pen devices for the treatment of adult patients with type-2 diabetes mellitus. These members voting "Yes" commented that their vote is contingent on the applicant working with the FDA to adequately address the labeling concerns mentioned during the discussion. The committee urged color differentiation between the two pens and objective mechanisms engineered into the pen devices to help prevent dosing errors. Most members recommended approval for patients already on prior treatment with one of the agents, though data on patients already using a GLP-1 agonist is lacking. In addition, the committee supports post-marketing studies targeting other sub-groups, such as African Americans, to assist in identifying a population who would benefit most from the combination product. While the committee members agreed that the drug combination is an approach for the management of adults with type 2 diabetes mellitus, an appropriate patient population was not clearly identified. One committee member was not present for the vote. Please see the transcript for details of the committee discussion.*

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

Committee Discussion: *The two committee members who voted “No” indicated that they voted “No” because of safety concerns and the probable dose errors presented by the labeling and the proposed pen devices. In addition, one member was concerned about off-label twice daily use due to use of insulin glargine as a twice daily injection in practice, and uncertainty with whether lixisenatide would be used as a twice daily injection. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 4:55 p.m.