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RESEARCH**

APPLICATION NUMBER:

208471Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # NDA 208471
Product Name: ADLYXIN (lixisenatide) injection

PMR #1 Description: Conduct a repeat dose, pharmacokinetic/pharmacodynamics (PK/PD) study evaluating Adlyxin (lixisenatide) in patients with type 2 diabetes ages 10 to 17 years (inclusive) that are insufficiently controlled with metformin and/or basal insulin. Subjects will be randomized to lixisenatide or placebo. Titration will occur every 2 weeks increasing the dose from 5 mcg to 10 mcg then to 20 mcg.

PMR #1 Schedule Milestones:	Study Completion:	<u>03/31/2018</u>
	Final Report Submission:	<u>09/30/2018</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Adlyxin is ready for approval for use in adults; however, pediatric studies had been deferred until adequate safety data were available from the adult program.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this PMR is to establish the PK/PD of Adlyxin in the pediatric population ages 10 to 17 years to determine appropriate dosing.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A repeat dose, pharmacokinetic/pharmacodynamics (PK/PD) study evaluating Adlyxin (lixisenatide) in patients with type 2 diabetes ages 10 to 17 years (inclusive) that are insufficiently controlled with metformin and/or basal insulin. Subjects will be randomized to lixisenatide or placebo. Titration will occur every 2 weeks increasing the dose from 5 mcg to 10 mcg then to 20 mcg.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
 - There is not enough existing information to assess these risks
 - Information cannot be gained through a different kind of investigation
 - The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
 - The trial will emphasize risk minimization for participants as the protocol is developed
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # NDA 208471
Product Name: ADLYXIN (lixisenatide) injection

PMR #2 Description: Conduct a 24-week, randomized, controlled efficacy and safety study comparing Adlyxin (lixisenatide) with placebo in patients with type 2 diabetes ages 10 to 17 years (inclusive), followed by a 28-week double-blind controlled extension. Subjects will be on a background of metformin and/or basal insulin at a stable dose. This trial should not be initiated until the results of the pediatric PK/PD study (PMR #1) have been submitted to and reviewed by the Agency.

PMR #2 Schedule Milestones:	Final Protocol Submission:	<u>03/31/2019</u>
	Study Completion:	<u>03/31/2024</u>
	Final Report Submission:	<u>09/30/2024</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Adlyxin is ready for approval for use in adults; however, pediatric studies had been deferred until adequate safety data were available from the adult program.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this PMR is to establish the safety and efficacy of Adlyxin in the pediatric population ages 10 to 17 years.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A 24-week, randomized, controlled efficacy and safety study comparing Adlyxin (lixisenatide) with placebo in patients with type 2 diabetes ages 10 to 17 years (inclusive), followed by a 28-week double-blind controlled extension. Subjects will be on a background of metformin and/or basal insulin at a stable dose. This trial should not be initiated until the results of the pediatric PK/PD study (PMR #1) have been submitted to and reviewed by the Agency.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 Pharmacokinetic studies or clinical trials
 Drug interaction or bioavailability studies or clinical trials
 Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 Are the objectives clear from the description of the PMR/PMC?
 Has the applicant adequately justified the choice of schedule milestone dates?
 Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # NDA 208471
Product Name: ADLYXIN (lixisenatide) injection

PMR #3 Description: Perform immunogenicity testing on anti-drug antibody (ADA)-positive samples from clinical studies of type 2 diabetes patients treated with lixisenatide to determine the incidence of neutralizing antibodies (NAb) and anti lixisenatide antibodies that are cross-reactive with endogenous GLP-1 and glucagon peptides and are capable of neutralizing these endogenous peptides. Assessments should be performed using assays demonstrated to be suitable for their intended purposes through formal validation studies that have been reviewed by the Agency prior to their use in clinical sample analysis. Samples used for these assessments should be archived under suitable conditions until testing, and should include sufficient quantity to allow for completion of required immunogenicity assessments. Study report(s) submitted to the Agency will include evaluation of the impact of NAb and cross-reactive antibodies on patient safety as well as PK, PD, and efficacy of lixisenatide.

PMR #3 Schedule Milestones:	Interim Milestone 1 (Final Report – Assay Validation)	<u>09/30/2017</u>
	Interim Milestone 2 (Studies EFC12404 and EFC12405 Completion)	<u>06/30/2018</u>
	Interim Milestone 3 (Studies EFC12404 and EFC12405 Final Report Submission)	<u>12/31/2018</u>
	Study Completion (EFC13794)	<u>01/31/2019</u>
	Final Study Report Submission (EFC13794)	<u>06/30/2019</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

There is a theoretical possibility that lixisenatide anti-drug antibodies that are cross-reactive with endogenous GLP-1 and glucagon may potentially be neutralizing, thereby aggravating problems in glucose metabolism.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Approximately 70% of clinical subjects tested positive for lixisenatide anti-drug antibodies (ADA) after treatment with lixisenatide for 24 weeks or more. Of these ADA-positive subjects, 28.4% were found to possess ADA cross-reactive with endogenous GLP-1 and 4.7% were cross-reactive with glucagon. These cross-reactivity results raise the possibility that the antibodies to lixisenatide may potentially neutralize the function of endogenous GLP-1 and glucagon. However, a comprehensive evaluation of ADA-positive T2DM samples for cross-reactivity utilizing a fully-validated assay was not performed. Therefore, there is residual concern that the neutralization of endogenous GLP-1 and glucagon by cross-reactive antibodies to lixisenatide may aggravate problems in glucose metabolism in lixisenatide-treated T2DM patients, including those who might later seek an alternative GLP-1 analog for their treatment. The PMR addresses these concerns by requiring the Sponsor to provide cross-reactivity assay validation, provide neutralizing antibody assay validation, assess neutralizing ADA response, and evaluate whether cross-reactive ADA are capable of neutralizing endogenous GLP-1 and glucagon.

3. If the study/clinical trial is a PMR, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Immunogenicity testing on anti-drug antibody (ADA)-positive samples from clinical studies of type 2 diabetes subjects, including validation of supportive ADA assays.

(b) (4)

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
Immunogenicity testing on anti-drug antibody (ADA)-positive samples from clinical studies of type 2 diabetes subjects, including validation of supportive ADA assays.
- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)
- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

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- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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/s/

JENNIFER R PIPPINS
07/27/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: July 25, 2016

To: Jean-Marc Guettier, MD
Director
Division of Metabolism and Endocrinology Products (DMEP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Nyedra W. Booker, PharmD, MPH
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Charuni Shah, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and
Instructions for Use (IFU)

Drug Name (established name): lixisenatide

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: NDA 208471

Applicant: sanofi-aventis U.S. LLC

1 INTRODUCTION

On July 27, 2015, sanofi-aventis U.S. LLC submitted for the Agency's review an Original New Drug Application (NDA) for lixisenatide injection, for subcutaneous use, NDA 208471. An NDA for lixisenatide was originally submitted on December 20, 2012 and was subsequently withdrawn on September 10, 2013.

Lixisenatide is proposed to be indicated as an adjunct to diet and exercise to improve glycemic control in the treatment of adults with type 2 diabetes mellitus with the following limitations of use:

- Has not been studied in patients with chronic pancreatitis or a history of unexplained pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.
- Not for treatment of type 1 diabetes or diabetic ketoacidosis.
- Has not been studied in combination with short acting insulin.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on September 11, 2015, for DMPP and OPDP to review the Applicant's proposed MG and IFU for lixisenatide injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft lixisenatide injection, for subcutaneous use MG received on July 27, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 20, 2016.
- Draft lixisenatide injection, for subcutaneous use Prescribing Information (PI) received on July 27, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 20, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFU document using the Arial font, size 10. In our collaborative review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)

- rearranged information due to conversion of the PI to Physicians Labeling Rule (PLR) format
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20.

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

MARCIA B WILLIAMS
07/25/2016

CHARUNI P SHAH
07/25/2016

LASHAWN M GRIFFITHS
07/25/2016

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: July 25, 2016

To: Martin White, Regulatory Project Manager
Division of Metabolism & Endocrine Products (DMEP)

From: Charuni Shah, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 208471
OPDP labeling comments for ADLYXIN (lixisenatide) injection, for subcutaneous use

On September 10, 2015, OPDP received a consult request from DMEP to review the proposed draft Prescribing Information (PI), Medication Guide, Instructions for Use (IFU), and carton/container labeling for ADLYXIN (lixisenatide) injection, for subcutaneous use. OPDP's comments on the proposed draft labeling are based on the version sent by Martin White via email on July 20, 2016, and are marked on the version provided directly below.

OPDP does not have any comments on the proposed carton/container labeling at this time.

Comments on the Medication Guide and IFUs are provided under a separate cover in a collaborative review between DMPP and OPDP.

Thank you for the opportunity to comment on this material.

If you have any questions, please contact Charuni Shah at 240-402-4997 or Charuni.Shah@fda.hhs.gov.

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/s/

CHARUNI P SHAH
07/25/2016

DATE: July 22, 2016

FROM: Robert Ball, MD, MPH, ScM,
Deputy Director, Office of Surveillance and Epidemiology, CDER, FDA

SUBJECT: Lixisenatide ARIA Sufficiency Memo

I concur with the lack of sufficiency of ARIA for evaluating anaphylaxis following Lixisenatide and make the following observations.

- 1) This memo focuses on the sufficiency of ARIA for “assessing signals of a serious risk”. I have also considered whether it might be useful to use ARIA to “identify unexpected serious risk when available data indicate potential for serious risk”. In this use the “unexpected serious risk” would be a higher risk of anaphylaxis than was identified in the trial data. In theory, it might be possible to use ARIA in this mode even if it wasn’t possible to use ARIA to make a rigorous inference around the risk or relative risk of anaphylaxis following Lixisenatide, by conducting surveillance only for a much higher risk. However, I conclude that the limitations described in the memo also preclude the use of ARIA for this use.
- 2) I also note that the issue of drug use discussed in this memo is a general issue for all new drugs. The special circumstances for this drug (e.g. many other drugs in the class already, low world-wide use) may not be relevant to other new drugs, and each case must be treated on its merits.

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)**

Epidemiology: ARIA Sufficiency Determination

Date: July 22, 2016

Reviewer: Christian Hampp, PhD
Division of Epidemiology I

Team Leader: Patricia L. Bright, MSPH, PhD,
Division of Epidemiology I

Deputy Division Director:
(Acting) Simone P. Pinheiro, ScD, MSc
Division of Epidemiology I

Subject: ARIA Sufficiency Memo: Lixisenatide and Anaphylaxis

Drug Name: lixisenatide

Application Type/Number: NDA 208471

Applicant/sponsor: Sanofi

OSE RCM #: 2016-1371

EXECUTIVE SUMMARY

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	
-Exposure	X
-Outcome(s) of Interest	X
-Covariate(s) of Interest	
-Surveillance Design/Analytic Tools	

1. BACKGROUND INFORMATION

1.1. Medical Product

On July 27, 2015, Sanofi submitted NDA 208471 for lixisenatide, a once-daily injectable glucagonlike peptide -1 (GLP-1) analog drug, as an adjunct to diet and exercise to improve glycemic control in the treatment of adults with type 2 diabetes mellitus. An NDA (NDA 204961) for lixisenatide was originally submitted to the FDA on December 20, 2012, but was subsequently withdrawn by the applicant. Lixisenatide was first approved in Mexico on January 7, 2013, and is currently approved in over 60 countries, including member states of the European Union. Five GLP-1 analogs are currently marketed in the United States (Table 1)

Table 1. GLP-1 analog drugs currently marketed in the United States

GLP-1 analog	Generic name	Date of approval
Byetta	exenatide	April 2005
Victoza	liraglutide	January 2010
Bydureon	exenatide ER	January 2012
Tanzeum	albiglutide	April 2014
Trulicity	dulaglutide	September 2014

On May 25, 2016, the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) recommended approval of lixisenatide with a 12-2 vote. However, committee members expressed concern about the imbalance in anaphylaxis reactions in the clinical trial development program.

On June 22, 2016, staff from OSE and the Office of New Drugs/Division of Metabolism and Endocrinology Products (OND/DMEP) conducted a Signal Assessment Meeting (SAM) to determine ARIA sufficiency for a study of lixisenatide and anaphylaxis.

1.2. Describe the Safety Concern

Imbalances in anaphylaxis rates were observed in the clinical development program for lixisenatide. Patients randomized to lixisenatide (n=7,874) experienced 16 events of anaphylaxis (0.20%) compared with 5 events among 4,842 patients randomized to placebo (0.10%).¹ When counting only anaphylaxis events that were deemed possibly related to the study drug by the adjudication committee, 10 events remained among patients randomized to lixisenatide and no events among patients randomized to placebo. Rates of urticaria or angioedema did not differ between groups.

Hypersensitivity reactions are included in the Warnings and Precautions sections of the labeling of all GLP-1 analog drugs. In addition, the labeling of exenatide, liraglutide, and exenatide ER, specifically mention anaphylaxis. However, unlike in the case of lixisenatide, anaphylaxis signals were only noted post-marketing for these marketed products. Of note, the clinical development program for taspoglutide (b) (4), another GLP-1 analog, was halted in phase 3 due to gastrointestinal adverse events and allergic reactions. Hypersensitivity was the most common systemic allergic reaction reported in 19 (5%) and 16 (4%) patients in the taspoglutide 10- and 20-mg groups, respectively, and in 3 (1%) patients in the exenatide group. Therefore, differences within the class are possible with respect to the intensity of the signal.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)

Assess a known serious risk	
Assess signals of serious risk	X
Identify unexpected serious risk when available data indicate potential for serious risk	

1.4. Statement of Purpose

The purpose of the proposed inferential analysis is to determine the risk of anaphylaxis reaction associated with the use of lixisenatide. FDA seeks to answer the question, "Given the imbalance noted in the pre-licensure data that was not identified in other drugs of this class, can Sentinel surveillance help clarify whether lixisenatide has a higher rate of anaphylaxis than other drugs of this class?" It is important to note that this is already an identified risk (i.e., a known adverse effect) and is well-labelled in the Warnings and Precautions of GLP-1 analog drugs, making the certainty of evidence needed much higher. Information gained may be used to inform labeling to provide more precise risk estimates, and to quantify whether this drug is substantively different than other drugs in the class. In this regulatory context, because the event of interest is rare, the sufficiency determination primarily rests upon the need for large sample sizes and high confidence of strong correlation between the electronic data and the actual clinical outcome.

1.5. Effect Size of Interest or Estimated Sample Size Desired

Please refer to Sections 3 and 4 for a discussion of factors that influence power and sample size.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

Skipped, given responses in Sections 3 and 4.

3. EXPOSURES

3.1. Treatment Exposure

The exposure of interest is lixisenatide.

3.2. Comparator Exposure(s)

Skipped, given responses in Sections 3 and 4.

3.3. Is ARIA sufficient to identify the exposure of interest?

ARIA was judged to be insufficient to identify adequate numbers of patients exposed to lixisenatide for study outcomes as rare as anaphylaxis (see Section 4). During the SAM, DMEP staff voiced concerns about potential market uptake, as a consequence of this drug being the 6th marketed GLP-1 analog, if approved, and its lack of superior clinical benefits that would make this a preferential choice as compared to other marketed GLP-1 analogs.

To explore other study options and to understand the use of lixisenatide relative to other GLP-1 analog drugs, staff from the Data Management and Analysis team in DEPI-I extracted crude counts of adult GLP-1 analog users in the U.K. CPRD database (Table 2). Of note, the time period differs between the individual drugs according to market availability. These data do not provide information on average or cumulative duration of use.

Table 2. Crude exposure counts for GLP-1 analog drugs in the CPRD database

GLP-1 analog	Time period	# of users
iraglutide	7/1/2009 - 6/15/2016	9,763
exenatide	12/1/2006 - 6/15/2016	6,506
exenatide ER	7/1/2011 - 6/15/2016	1,738
ixisenatide	2/1/2013 - 6/15/2016	1,295
dulaglutide	12/1/2014 - 6/15/2016	127
albiglutide	3/1/2014 - 6/15/2016	none

After applying inclusion, exclusion, and possibly, matching criteria, a study based on the CPRD would likely include fewer exposed patients than those shown in Table 2.

Furthermore, as of September 30, 2015, the worldwide cumulative patient exposure to lixisenatide reached only approximately 61,000 person-years in 60 countries.² This limited exposure to date limits study options, even if multiple databases were to be combined.

4. OUTCOMES

4.1. Outcomes of Interest

The outcome of interest is anaphylaxis.

4.2. Is ARIA sufficient to assess the outcome of interest?

ARIA was judged to be insufficient to assess the outcome of interest in this particular case. Three main concerns exist: (1) low frequency of events, and (2) inadequate/uncertain validity of algorithms to ascertain anaphylaxis, and (3) limited ability to establish temporal proximity between exposure and outcome.

First, during the clinical development program, the sponsor detected anaphylaxis events at a rate of 2 per 10,000 person-years (placebo) and ^{(b) (4)} per 10,000 person-years (lixisenatide).^{2, a} In an analysis of ^{(b) (4)} commercial claims data, anaphylaxis occurred at a rate of ^{(b) (4)} per 10,000 person-years in a cohort of GLP-1 analog (exenatide, liraglutide, albiglutide, dulaglutide) users.² To achieve adequate power to study an event as rare as anaphylaxis would require a sample size that may not become available in Sentinel for many years. Indeed, a study of the uptake of newly approved drugs in Mini-Sentinel found that “[t]here is limited ability to detect rate ratios below three for events with background rates of 1/1000 person-years or lower.”³ Of note, this statement was made in the context of ascertaining precise estimates in the early postmarket phase (2-3 years) and available exposure counts may increase with longer time since approval.

Second, the validity of ascertaining anaphylaxis events based on ICD-9-CM codes is questionable and the validity of using ICD-10 codes has not been evaluated. A validation study conducted by Walsh et al. found a positive predictive value (PPV) of 63.1% for an algorithm to detect anaphylaxis in Mini-Sentinel data.⁴ An algorithm that combined both anaphylaxis and serious allergic reaction had a PPV of 76.2%, but that algorithm was developed *post-hoc* and is therefore not validated. FDA epidemiologists conducted two studies of anaphylaxis reaction following iron supplementation using the Walsh algorithm: a published study based on CMS data⁵ and a ^{(b) (4)}. In the CMS study, the authors added exposure to the case definition and restricted the risk window to the same day as the exposure in an attempt to increase PPV. These options may not be appropriate in the case of lixisenatide because anaphylaxis events in the clinical trials tended to occur early, but not on the day of drug initiation. Wang et al. conceded that the sensitivity of their approach may still be low. ^{(b) (4)}

In addition, a study of lixisenatide and anaphylaxis would ascertain outcomes based on ICD-10 codes, but the validity of using ICD-10 codes to detect anaphylaxis events has not been evaluated. Although chart review may be able to provide adjudicated events for the subset of patients with available charts, it may not yield an algorithm with adequate validity that could be applied to all potential cases.

^a These event rates were provided by the sponsor to support a comparison of clinical trial rates with those of other GLP-1 analogs based on ^{(b) (4)} commercial claims data. The rates were calculated based on ^{(b) (4)} lixisenatide) vs. 2 (placebo) anaphylaxis events that were not adjudicated.

At the SAM, OSE and OND/DMEP staff also considered alternative endpoints with better validity, which could potentially serve as proxies for anaphylaxis. Such examples included angioedema and urticaria. However, no imbalances in adjudicated angioedema events (lixisenatide, 0.10% vs. placebo, 0.12%) or urticaria (lixisenatide, 0.34% vs. placebo, 0.29%) were observed in the lixisenatide clinical trials, thus calling into question the utility of studying these as proxy endpoints.

Third, although, as mentioned above, anaphylaxis events in the clinical trials typically did not occur with the first dose, they did occur within in minutes of a lixisenatide injection. However, a claims-based analysis would ascertain exposure based on prescription fill date and days of supply, and could not establish when a patient actually injected a single dose in relation to the timing of an anaphylaxis event. This could result in misspecification of the exposure risk-window and bias the study, most likely toward no effect. Studies based on medical records (subject to sample size limitations) or spontaneous reports would presumably be better suited to establish temporal proximity between exposure and outcome.

5. COVARIATES

Skipped, given responses in Sections 3 and 4.

6. SURVEILLANCE DESIGN / ANALYTIC TOOLS

Skipped, given responses in Sections 3 and 4.

7. NEXT STEPS

On June 16, 2016, the sponsor submitted to the FDA a brief outline (b) (4)

[Redacted]

[Redacted] (b) (4)

DEPI-I recommendation

For the reasons outlined in this memo, DEPI-I staff concludes that, based on current assumptions, large observational studies are likely inadequate to assess an association between lixisenatide and anaphylaxis reactions. If approved, we recommend that the FDA pharmacovigilance team monitor signals of anaphylaxis reactions with lixisenatide with the

methodology it deems the most appropriate. In addition, lixisenatide market uptake and utilization should be monitored. If additional signals of anaphylaxis or similar reactions emerge, and/or lixisenatide utilization exceeds expected levels, a determination of ARIA sufficiency or a PMR study option should be revisited, based on that new safety information.

8. REFERENCES

- 1 FDA Briefing Document, Endocrinologic and Metabolic Drugs Advisory Committee Meeting, May 25, 2016, Page 41. Adapted from Table 67 of the Integrated Summary of Safety for NDA 208471.
<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM502558.pdf>, accessed 7/15/2016.
- 2 Hampp C., Review of sponsor's comparison of anaphylaxis and hypersensitivity event rates among patients exposed to lixisenatide in clinical trials to rates from an external population. Available in DARRTS, April 7, 2016.
- 3 Mott K et al. Uptake of new drugs in the early post-approval period in the Mini-Sentinel distributed database. *Pharmacoepidemiol Drug Saf.* 2016 May 4. [Epub ahead of print]
- 4 Wash KE et al. Validation of anaphylaxis in the Food and Drug Administration's Mini-Sentinel. *Pharmacoepidemiol Drug Saf.* 2013 Nov;22(11):1205-13.
- 5 Wang C et al. Comparative risk of anaphylactic reactions associated with intravenous iron products. *JAMA.* 2015 Nov 17;314(19):2062-8.

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/s/

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**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research**

Office of Biotechnology Products
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Date: 06/20/2016
Primary Reviewer: Faruk Sheikh, Ph.D., Senior Staff Fellow, OBP, DBRR-2
Secondary Reviewer: Harold Dickensheets, Ph.D., Staff Scientist, OBP, DBRR-2
Consult: Immunogenicity Review
 For Division of Metabolism and Endocrinology Products

Application Number: NDA 208471

Product Name: Lixisenatide, a Synthetic 44-Amino Acid Peptide with six C-terminal Lys residues (b) (4)

Indication: Type II Diabetes Mellitus (T2DM)

Route of Admin: SC Injection to be taken once daily within one hour prior to (b) (4) the first meal of the day (b) (4) from a prefilled pen.

Sponsor: Sanofi US Services Inc.

AC committee meeting: 05/25/2016

Dates for Review Process:

Consult received: 02/24/2016
 IR request: 03/21/2016
 Response received: 03/29/2016
 Second IR request: 04/15/2016
 Response received: 05/04/2016
 Update received: 05/23/2016

Review Team:

Clinical: Suchitra Balakrishnan
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I. SUMMARY BASIS OF RECOMMENDATION:

a. Recommendation:

Approximately 70% of clinical subjects tested positive for lixisenatide anti-drug antibodies (ADA) after treatment with lixisenatide for 24 weeks or more. Of these ADA-positive subjects, 28.4% were found to possess ADA cross-reactive with endogenous GLP-1 and 4.7% were cross-reactive with glucagon, likely due to the predicted similarities in portions of the peptide amino acid sequence between lixisenatide and endogenous GLP-1 and glucagon counterparts. The cross-reactivity results raise the possibility that the antibodies to lixisenatide may potentially neutralize the function of endogenous GLP-1 and glucagon. Therefore, there is residual concern that the

neutralization of endogenous GLP-1 and glucagon by cross-reactive antibodies to lixisenatide may aggravate the problems in glucose metabolism in lixisenatide-treated T2DM subjects, including those who might later seek an alternative GLP-1 analog for their treatment. In light of this, we recommend that the sponsor; 1) provide a formal report of the cross-reactivity assay validation and the assay SOP's, 2) submit lixisenatide neutralizing antibody (NAb) assay validation and assay SOP's, 3) assess neutralizing ADA response that are expected to be present in patient samples using validated neutralizing antibody assay, and 4) evaluate whether cross-reactive ADA are capable of neutralizing endogenous GLP-1 and glucagon. Pending concurrence from the clinical team, these recommendations can be fulfilled as PMR.

b. Justification:

Lixisenatide is a non-human synthetic peptide. The sponsor used a validated anti-lixisenatide antibody binding assay (DARRTS Reference ID: 3373058; September 13, 2013) to analyze clinical samples, which indicated that Lixisenatide is highly immunogenic. The lixisenatide-ADA incidence was found to be 70% in study subjects who were treated with lixisenatide for more than 24 weeks. The safety and efficacy data analysis indicates that the group of lixisenatide treated subjects with anti-lixisenatide antibody concentrations >100nmol/L exhibits a significantly different response in HbA1c (glycated hemoglobin) when compared to patients with low ADA levels or no antibodies ([Table 2](#) and [Table 3](#)). The cross-reactivity test results provided by the sponsor showed that serum samples from 28.4% of ADA-positive subjects cross-react with endogenous GLP-1, and that 4.7% of ADA-positive samples cross-react with glucagon. These cross-reactive ADA might potentially neutralize the activities of endogenous GLP-1 and glucagon in glucose homeostasis. The sponsor did not test whether the HbA1c response difference was due to neutralization of the endogenous GLP-1, glucagon or the lixisenatide peptide. In order to determine whether the HbA1c response difference could be related to the neutralization of endogenous GLP-1, glucagon or lixisenatide activity, further data are required concerning the neutralizing activity of these ADAs.

II. COMMENTS TO SPONSOR:

N/A.

III. REVIEW

1. Executive summary:

The analytical procedure for the detection of anti-lixisenatide antibodies in human serum has been validated earlier under NDA submission NDA204961 (DARRTS Reference ID: 3373058; September 13, 2013). The application was first submitted on December 20, 2012 and subsequently withdrawn on September 10, 2013 and later resubmitted as

a new application (NDA208471) on July 27, 2015. The current immunogenicity consult request for lixisenatide was received on February 24, 2016.

Anti-lixisenatide antibody (ADA) data collected by the sponsor from nine Phase 3 placebo-controlled pivotal studies (EFC6014, EFC6015, EFC6016, EFC6017, EFC6018, EFC10743, EFC10781, EFC10887, and EFC11321) indicated that the percentage of binding antibody-positive patients in the lixisenatide group increased over the length of exposure of the drug. There were 57.7% (n=101/175) subjects (T2DM, type II diabetic) testing positive for the presence of ADA at week 12, 69.6% (n=1370/1968) subjects testing positive after 24 weeks of treatment and 71.5% (n=913/1277) subjects testing positive after 76 weeks of treatment (see [Table 1](#) below). The overall incidence of anti-lixisenatide ADA in the trial subjects remained at approximately 70%.

The sponsor provided data from a meta-analysis with respect to change in efficacies (change in HbA1c) for subjects treated with lixisenatide for 24 weeks and 76 weeks. The results indicated that a substantial number of trial subjects exhibit significantly different responses in HbA1c when compared to subjects with lower concentrations (<100nmol/L) or no antibodies against lixisenatide ([Table 2](#) (24 weeks) and [Table 3](#) (76 weeks)). There is a potential that the lixisenatide peptide may induce formation of NAb as a subset of the binding Ab, which could affect efficacy of the study drug by interfering with its recognition by the target receptor. The sponsor did not test for the presence of NAb against lixisenatide. Therefore the clinical review team raised concerns about the possibility of neutralizing antibodies (NAb) in these subjects, which initiated this immunogenicity consult.

Because lixisenatide shares a high degree of amino acid sequence homology with human GLP-1 and glucagon in the first 12 amino acids (as shown in [Figure 1](#)), the immunogenicity reviewer remains concerned that exposure to lixisenatide over time may potentially lead to the development of ADAs able to cross-react with endogenous GLP-1 and glucagon. The potential exists for these cross-reactive ADA to impact glucose metabolism through neutralization of the subject's endogenous GLP-1 and/or glucagon. In order to understand the potential impact of cross-reactive ADA's, cross-reactivity data were initially requested for the subset of patients discussed above (those with decreased lixisenatide clinical efficacy associated with higher levels of ADA). The sponsor addressed subsequent IR and provided numerical data for all subjects assessed for cross-reactivity, rather than the qualitative (positive or negative) scoring initially provided. These subsequent data, and the sponsor's self-initiated re-evaluation of the cross-reactivity assay cut point revealed the presence of substantial incidences of lixisenatide ADA cross-reactive with endogenous GLP-1 (28.4%, 361/1269) and glucagon (4.7%, 60/1269).

Reviewer Comment: *The sponsor's reported cross-reactivity incidence may not reflect the actual incidence, since in my opinion the validation data submitted may be insufficient; this will be determined, with clinical reviewer concurrence, through review*

of required post-marketing assay validation data and evaluation of the neutralizing capacity of the ADA cross-reactive with endogenous GLP-1 and glucagon. The sponsor will also be required to report cross-reactivity in the labeling. Regardless, in my opinion, data from the sponsor's cross-reactivity evaluation provide sufficient cause for a safety issue to require further evaluation.

2. Product Background:

Lixisenatide, also known as AVE0100, is under development by Sanofi-Aventis for the treatment of T2DM. Lixisenatide binds to human glucagon-like peptide-1 receptor (GLP-1R) and activates biological activities similar to human GLP-1 that increases postprandial insulin secretion from the pancreas.

The structure of lixisenatide was based on exendin-4 (1-39) with a few amino acid modifications. Exendin-4 is also a GLP-1 analog, originally isolated from the saliva of a mountain lizard (*Heloderma suspectum*). (b) (4) and six lysine residues are added to the C-terminus of exendin-4 to generate lixisenatide. These modifications were made to enable the product to withstand physiological degradation by dipeptidyl peptidase IV. Both exendin-4 (exenatide) and lixisenatide show a high degree of homology with the first 12 amino acids of human GLP-1 and glucagon ([Figure 1](#)).

Lixisenatide: HEGTFTSDL**SKQME**EEAVRL**FI**E**WL**K**NG**GPSSGAPPS (K)₆
Exenatide: HEGTFTSDL**SKQME**EEAVRL**FI**E**WL**K**NG**GPSSGAPPPS
Human GLP-1: HAEGTFTSDVSSYLE**EGQA**KE**FI**AWLVKGRG
Glucagon: HS**Q**GTFTSDY**SKY**LDSRR**AQ**DFV**Q**WLMNT

Fig1: Amino acid (AA) sequence of lixisenatide, exendin-4, human GLP-1 and glucagon. AA homology of GLP-1 and glucagon with lixisenatide are shown in blue font.

Lixisenatide demonstrated affinity and selectivity for the human GLP-1 receptor in preclinical studies, with approximately 4-fold higher binding than that of native GLP-1^{1,2,3}. The mean terminal half-life of lixisenatide is approximately 3 hours in patients with type 2 diabetes and the time to T_{max} is 1-3.5 hours.

¹ Thorkildsen C, Neve S, Larsen BD, Meier E, Petersen JS (2003): Glucagon-like peptide 1 receptor agonist ZP10A increases insulin mRNA expression and prevents diabetic progression in db/db mice. *J Pharmacol Exp Ther.* 307(2):490-6.

² Christensen M, Knop FK, Holst JJ, Vilsbøll T. (2009): Lixisenatide, a novel GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus. *IDrugs*, Aug;12(8):503-13.

³ Elkinson S and Keating GM (2013): Lixisenatide: First Global Approval, *Drugs*, 73:383-391.

3. Immunogenicity results and risk analysis:

ADA incidence:

Lixisenatide is a non-human protein; therefore human subjects may potentially develop antibodies to lixisenatide during the course of treatment. The incidence of anti-lixisenatide antibodies has been assessed in nine placebo-controlled Phase 3 clinical studies. The results indicate that 70% of T2DM patients developed binding antibodies (BAb) following lixisenatide treatment for more than 24 weeks ([Table 1](#), below). Therefore, this product is both highly immunogenic and shares a high degree of homology with the N-terminal 12 amino acids of human GLP-1 and glucagon ([Figure 1](#)), raising the possibility of cross-reactive antibodies among the lixisenatide ADA.

Table 1- Number (%) of patients with anti-lixisenatide antibody status by visit in Phase 3 placebo-controlled studies: entire treatment period - safety population

Visit	Antibody Status, n/N1 (%)	Placebo (N=1639)	Lixisenatide (N=2869)
Baseline	Positive	52/1484 (3.5%)	129/2515 (5.1%)
	Negative	1432/1484 (96.5%)	2386/2515 (94.9%)
Week 2	Positive	59/1419 (4.2%)	232/2406 (9.6%)
	Negative	1360/1419 (95.8%)	2174/2406 (90.4%)
Week 4	Positive	67/1409 (4.8%)	879/2354 (37.3%)
	Negative	1342/1409 (95.2%)	1475/2354 (62.7%)
Week 12	Positive	3/93 (3.2%)	101/175 (57.7%)
	Negative	90/93 (96.8%)	74/175 (42.3%)
Week 24	Positive	103/1318 (7.8%)	1370/1968 (69.6%)
	Negative	1215/1318 (92.2%)	598/1968 (30.4%)
Week 76	Positive	29/596 (4.9%)	913/1277 (71.5%)
	Negative	567/596 (95.1%)	364/1277 (28.5%)
Week 100	Positive	3/133 (2.3%)	226/322 (70.2%)
	Negative	130/133 (97.7%)	96/322 (29.8%)

N = the number of patients in the safety population.

N1 = the number of patients with evaluable anti-lixisenatide antibody status in the safety population at the respective visit.

Data Pool 1: EFC6014, EFC6015, EFC6016, EFC6017, EFC6018, EFC10743, EFC10781, EFC10887, and EFC11321.

PGM=PRODOPS/AVE0010/OVERALL/CTD_2015_LIXI/REPORT/PGM/ab_statusbyvisit_t.sas

OUT=REPORT/OUTPUT/ab_statusbyvisit_t_p3pc_i.rtf(18JUN2015 - 9:02)

Source: Integrated Summary of Safety: AVE0010 – lixisenatide; Version number:1 06-Jul-2015.

Reviewer Comment: The table above, copied from the Clinical Summary of Efficacy section of the submission demonstrates that although a small increase in binding

antibody (BAb) incidence can be detected during the second week of treatment, by Week 4 the incidence had increased strongly, reaching a plateau of approximately 70% incidence at Week 24 which was maintained through Week 100.

Neutralizing ADA (NAb assessment)

Despite the relatively high incidence of lixisenatide ADA detected in the binding antibody (BAb) assessment, the sponsor did not submit results from assessment of the presence of neutralizing antibodies (NAb). The clinical reviewer noted a potential association between the presence of higher levels of ADA (>100 nmol/L) in some lixisenatide-treated subjects and a lower efficacy (decreased effect on HbA1c change from baseline) as shown in the table 2 & 3 below (circled with red dashed line), which was one reason for the immunogenicity consult. This decrease in efficacy could be the result of NAb. This deficiency was addressed in the first (March 21, 2016) IR, as discussed below.

Table 2- Meta analysis of change in HbA1c (%) from baseline to Week 24 by anti-lixisenatide antibody status and concentration based on pooled data of 8 pivotal phase 3 placebo-controlled studies - mITT population

	Lixisenatide			
	n/N (%)	LS Mean ^b	SE ^b	95% C.I. ^b
Anti-lixisenatide antibody status ^a				
Positive	1333/1954 (68.2%)	-0.82	0.036	(-0.895 to -0.755)
Negative	621/1954 (31.8%)	-0.83	0.044	(-0.920 to -0.746)
Anti-lixisenatide antibody concentration ^c				
Antibody negative	621/1890 ^d (32.9%)			
<LLOQ	854/1890 ^d (45.2%)	-0.88	0.043	(-0.963 to -0.796)
Total antibody negative or <LLOQ	1475/1890 ^d (78.0%)	-0.86	0.035	(-0.930 to -0.795)
≥ LLOQ	415/1890 ^d (22.0%)	-0.63	0.050	(-0.732 to -0.534)
≤100 nmol/L	370/1890 ^d (19.6%)	-0.64	0.057	(-0.751 to -0.528)
>100 nmol/L	45/1890 ^d (2.4%)	-0.16	0.131	(-0.418 to 0.096)

LLOQ = Lower limit of quantification (3.21 nmol/L); n = number of subjects, N = total number of subjects with available data; SE = standard error.

^a The denominator is number of patients with HbA1c (%) and anti-lixisenatide antibody status data collected on the same date.

^b A fixed-effect meta-analysis method with the inverse of variance as the weight was used for the pooled data of EFC6014, EFC6015, EFC6016, EFC6017, EFC10743, EFC10781, EFC10887 and EFC11321.

^c Based on patients with HbA1c and anti-lixisenatide antibody concentration collected on the same date.

^d Total patients with available data (either a negative antibody status or a measured antibody concentration, plus an available HbA1c measurement). This number includes 173 patients that have antibody concentration data with missing antibody status and also includes 237 patients that have antibody-positive status with missing antibody concentration.

Week 24 value is the last observation carried forward (LOCF) before initiation of rescue therapy on or before week 24.

Source: Clinical Summary of Efficacy: AVE0010 – lixisenatide - Version number: 1 19-Jun-2015 – Table 23.

Table 3- Meta analysis of change in HbA1c (%) from baseline to Week 76 by anti-lixisenatide antibody status and concentration based on the pooled data of 5 pivotal phase 3 placebo – mITT population

	Lixisenatide			
	n/N (%)	LS Mean ^b	SE ^b	95% C.I. ^b
Anti-lixisenatide antibody status ^a				
Positive	656/ 960 (68.3%)	-0.69	0.046	(-0.781 to -0.602)
Negative	304/ 960 (31.7%)	-0.96	0.059	(-1.071 to -0.842)
Anti-lixisenatide antibody concentration ^c				
Antibody negative	304/ 957 ^d (31.8%)			
<LLOQ	374/ 957 ^d (39.1%)	-0.92	0.055	(-1.031 to -0.818)
Total antibody negative or <LLOQ	678/ 957 ^d (70.8%)	-0.91	0.044	(-1.002 to -0.827)
≥ LLOQ	279/ 957 ^d (29.2%)	-0.50	0.060	(-0.617 to -0.380)
≤100 nmol/L	249/ 957 ^d (26.0%)	-0.58	0.064	(-0.701 to -0.449)
>100 nmol/L	30/ 957 ^d (3.1%)	-0.52	0.170	(-0.853 to -0.188)

LLOQ = Lower limit of quantification (3.21 nmol/L); n = number of subjects; N = total number of subjects with available data; SE = standard error.

^a The denominator is number of patients with HbA1c (%) and anti-lixisenatide antibody status data collected on the same date at week 76.

^b A fixed-effect meta-analysis method with the inverse of variance as the weight was used for the pooled data of EFC6014, EFC6015, EFC6016, EFC6017 and EFC10743.

^c Based on patients with HbA1c and anti-lixisenatide antibody concentration collected on the same date at week 76.

^d Total patients with available data (either a negative antibody status or a measured antibody concentration, plus an available HbA1c measurement). This number includes 14 patients that have antibody concentration data with missing antibody status and also includes 17 patients that have antibody-positive status with missing antibody concentration.

The change in HbA1c from baseline to week 76 is based on the observed value from the week 76 visit prior to the introduction of rescue medication and/or after the treatment cessation plus 3 days.

Source: Clinical Summary of Efficacy: AVE0010 – lixisenatide - Version number: 1 19-Jun-2015 – Table 24.

Reviewer Comment: *These meta-analysis data indicate that there is a potential association between the presence of higher levels of ADA (>100 nmol/L) and a lower efficacy which is measured by HbA1c content (primary endpoint) in some lixisenatide-treated subjects. At 24 weeks of treatment (Table 2), about 2.4% of patients (n=45/1890), showed a significant change in HbA1c to -0.16% in comparison to baseline (-0.86%). At 76 weeks, the change in Hba1c was observed in 30 of 957 ADA-positive patients (3.1%) who had ADA concentration >100 nmol/L. The change in HbA1c content in these patients was 0.52% while at baseline the HbA1c content was -0.96%. These differences in HbA1c could indicate the development of neutralizing antibodies in patients who developed high concentration of ADAs after lixisenatide treatment for 24 weeks or more. Although NAb assay would have been recommended to further characterize the binding antibodies detected during the review performed for the first NDA submission (NDA#204961) since anti-lixisenatide binding antibodies had been detected, this request was not communicated to the sponsor due to withdrawal of the NDA.*

ADA Cross-reactivity

The sponsor performed cross-reactivity testing for subjects in three Phase 3 studies (studies EFC10781, EFC11321 and EFC6015). The initial report for ADA cross-reactivity with endogenous GLP-1 and glucagon contained only a subjective “Positive/Negative” data calling, with no supporting numerical data. This deficiency in supportive primary data submission was addressed in an information request, as discussed below.

In response to the immunogenicity deficiency comment, the sponsor determined a new specificity cut-point for GLP-1 and glucagon cross-reactivity analyses using samples from lixisenatide ADA-negative subjects from their studies. The summary data presented in the reviewer-prepared [Table 4](#) (below) demonstrate the presence of anti-lixisenatide antibodies cross-reactive with the endogenous GLP-1 (28.4% of ADA-positive subjects) and glucagon (4.7% of ADA-positive subjects) raising a concern that neutralizing antibodies (NAb) to lixisenatide, if present, could cause a functional depletion of the endogenous peptide hormones in treated subjects. In addition, these antibodies could also affect those who discontinue lixisenatide treatment and seek an alternative GLP-1 analog for their treatment, depending on how long the cross-reactive ADAs persist after cessation of treatment. This potential neutralizing effect of anti-lixisenatide antibodies to human GLP-1 and glucagon function, if verified, may impact the safety and efficacy of lixisenatide.

Table 4: Cross-reactivity of anti-lixisenatide antibodies to endogenous GLP-1 and Glucagon in EFC6015, EFC10781 and EFC11321 studies

	Specificity Cut-point	n/N	% cross-reactivity
GLP-1	5.657%	361/1269	28.4
Glucagon	6.499%	60/1269	4.7

n= number of subjects tested positive for antibodies cross-reacting with anti-lixisenatide antibodies

N= total number of subjects in studies EFC6015, EFC10781 and EFC11321

Source: Adapted from Clinical response to agency request – 11 May 2016

Reviewer Comment: *The sponsor resubmitted a brief summary of the cross-reactivity assay, performed as part of the binding antibody assay validation package previously submitted under original NDA204961, in response to the recent Agency request (IR date 05-04-2016) for cross-reactivity assay validation studies during review of the current NDA208471. The sponsor re-evaluated the assay cut points for the endogenous GLP-1 and glucagon cross-reactivity assay, using in-study lixisenatide ADA-negative samples from 3 of their 9 clinical trials (see below for more details). However, in my opinion, the cross-reactivity assay “validation” information is sparse, and not fully validated to demonstrate sensitive detection of ADA cross-reactive with endogenous GLP-1 or glucagon, and the specificity cut points for the cross-reactivity assays (5.657% and 6.499% inhibition of lixisenatide binding by GLP-1 and glucagon, respectively) seem very low. In my experience, competition assays similar to this typically use a higher percent inhibition as the cut point. In general the sponsor’s data are indicative of the presence of*

a potentially significant incidence of ADA cross-reactivity with endogenous GLP-1 and glucagon in subjects treated with lixisenatide, pending clarification of the validation status of the assay (post-approval, if approved).

4. Information requests to sponsor:

a) Immunogenicity deficiency Comments sent to the sponsor on March 21, 2016

Your 24 week meta-analysis of change in HbA1c (Table 2) indicates that a small group of the lixisenatide treatment population (n=45, 2.4%) with anti-lixisenatide antibody concentrations >100nmol/L exhibits a significantly different response in HbA1c when compared to patients with low levels or no antibodies.

Similarly, the meta-analysis of change in HbA1c at week 76 using long-term data from five pivotal phase 3 studies (EFC6014, EFC6015, EFC6016, EFC6017 and EFC10743) indicates that significant numbers of anti-lixisenatide antibody positive patients (n=279/957; 29.2%) exhibit significantly different responses in HbA1c as compared to responses observed in ADA-positive patients (n=304/906, 31.7%).

Since lixisenatide and human GLP-1/glucagon share considerable amino acid sequence homology in the first 12 amino acids, the potential exists that exposure to lixisenatide may lead to the development of anti-drug antibodies (ADA) that cross-react with endogenous GLP-1 and or glucagon. In order to determine whether the HbA1c response difference could be related to changes in endogenous GLP-1 or glucagon activity anti-lixisenatide, antibody cross-reactivity data for these patients are needed. We could not find these data in your submission. Therefore, we request the following information for clarification:

- 1) Submit cross-reactivity testing data for the 45 patients with anti-lixisenatide antibody concentration >100nmol/L (Table 23) and 279 patients with ADA concentration \geq LLOQ at Week 76 (Table 24) with endogenous GLP-1 and glucagon. Data should include tabular summary of these results organized by patient across the study timeline, if anti-lixisenatide cross-reactivity has been assessed at multiple time points.*
- 2) Please include anti-lixisenatide antibody titers for each of these samples expressed both as a dilution ratio and as the mass units previously provided.*
- 3) To better understand the clinical impact of the observed anti-lixisenatide antibodies, in the absence of information regarding the presence of anti-lixisenatide neutralizing antibodies (NAb), please submit an assessment for correlations between PK and PD effects observed with the relative abundance of ADA in lixisenatide-treated subjects.*

If anti-lixisenatide antibodies from your clinical trial samples correlate with observed adverse clinical effects, or demonstrate cross-reactivity with endogenous GLP-1

and/or glucagon, you may be required to test for the presence of neutralizing antibodies (NAb) using a validated NAb assay. Further, if cross-reactivity with endogenous GLP-1 or glucagon is demonstrated in samples from extended lixisenatide administration (76 weeks or later), the potential for development of a deficiency in one or both of these cross-reactive endogenous targets should be evaluated. Provide a plan to develop a NAb assay in the event that such studies are required.

b) Sponsor's response to immunogenicity comments received on March 29, 2016:

FDA comment 1: Submit cross-reactivity testing data for the 45 patients with anti-lixisenatide antibody concentration >100nmol/L (Table 23) and 279 patients with ADA concentration \geq LLOQ at Week 76 (Table 24) with endogenous GLP-1 and glucagon. Data should include tabular summary of these results organized by patient across the study timeline, if anti-lixisenatide cross-reactivity has been assessed at multiple time points.

Sponsor's Response: "In the lixisenatide phase 3 program, the cross-reactivity of anti-lixisenatide antibody (ADA) to endogenous GLP-1 or glucagon was assessed in 3 studies (EFC10781, EFC11321 and EFC6015). Cross-reactivity was investigated in samples with a confirmed ADA positive status at the main efficacy endpoint (Week 24, or end-of-treatment visit or pre-rescue visit in case of treatment discontinuation or rescue before Week 24). 18 of the 45 patients with anti-lixisenatide concentrations >100 nmol/L listed in Table 23 (SCE Module 2.7.3) were part of one of these 3 studies. The remaining 27 patients were enrolled in studies where cross reactivity was not assessed.

As outlined in the study protocols, cross-reactivity was not assessed at multiple time points or after Week 24. However, a few patients had cross-reactivity assessed on more than 1 occasion and/or after Week 24 due to protocol deviations.

Table 3 below shows the ADA concentration and cross-reactivity data for the 194 patients who had an ADA concentration \geq LLOQ (3.21nmol/L) concomitantly with cross-reactivity assessment, including 18 patients (flagged in the right column) who had an ADA concentration >100nmol/L.

It confirms the absence of cross-reactivity of anti-lixisenatide antibodies, at the end of the main treatment period, to endogenous GLP-1 and glucagon in all patients with ADA concentrations \geq LLOQ".

Reviewer comment:

The sponsor submitted qualitative cross-reactivity assay results (positive or negative scoring) obtained from 3 of 9 phase 3 studies (EFC10781, EFC11321 and EFC6015). None of the subjects were reported to exhibit cross-reactivity with endogenous GLP-1 and glucagon by the initial scoring method according to the sponsor's evaluation.

The sponsor tested cross-reactivity in 18 of the 45 subjects at week 24 ([Table 5](#) and [Table 6](#)) that showed differential responses with respect to HbA1c. Although these subjects show different responses in primary efficacy endpoint (HbA1c), the sponsor stated that none of these 18 subjects show cross-reactivity with endogenous GLP-1 or glucagon. The antibody concentration of these patients was between 100-275nmol/L except one subject who had antibodies concentration 1840nmol/L at end-of-treatment (EOT) visit.

Table 5: ADA status of subjects (n=18/45) that show significant change in HbA1c

	Subject ID	ADA conc. (nmol/L)		Subject ID	ADA conc. (nmol/L)
1	010781-032-201-004	228	10	011321-156-031-017	133
2	010781-124-219-003	158	11	006015-158-503-005	172
3	010781-348-203-013	128	12	006015-158-504-008	134
4	010781-356-206-020	171	13	006015-158-504-011	103
5	010781-616-206-009	194	14	006015-356-503-023	123
6	010781-840-201-010	135	15	006015-356-506-009	121
7	010781-840-212-004	V70 EOT/1840	16	006015-392-528-003	121
8	011321-156-010-028	275	17	006015-410-505-001	125
9	011321-156-031-018	195	18	006015-840-520-014	150

Source: The table is created from the results submitted with the response to agency request on March 29, 2016.

Table 6: Number of subjects tested for cross-reactivity of ADAs with endogenous GLP-1 and Glucagon

24 weeks or less (n=413)	Tested at the following Visits	No. of subjects	Cross-reactivity results with	
			Endogenous GLP-1	Glucagon
	Week 4	14 subjects	Negative	Negative
	Week 13	220 subjects	Negative	Negative
	Visit 12/Week 24	125 subjects	Negative	Negative
	Visit 22/Week 24	54 subjects	Negative	Negative
≥ 24 weeks (n=18)	Visit 70 /EOT visit	7 subjects	Negative	Negative
	Visit 80/Pre Rescue	6 subjects	Negative	Negative
	Visit 99	3 subjects	Negative	Negative
	Visit 19/Week 52	1 subject	Negative	Negative
	Visit 21/Week 60	Same subject	Negative	Negative
	Visit 23/Week 68	Same subject	Negative	Negative
	Visit 25/Week 76	1 subject	Negative	Negative
	Visit 31/Week 100	Same subject	Negative	Negative

Source: The table is created from the results submitted with the response to agency request on March 29, 2016.

The sponsor also submitted ADA cross-reactivity data from subjects who were administered lixisenatide for more than 24 weeks and who developed antibodies <100nmol/L. After 76 weeks of lixisenatide treatment, 26% of patients (n=249/957) developed antibodies at the concentration of <100nmol/L and approximately 3.1% (n=30/957) of patients developed antibodies >100nmol/L. The sponsor did not submit ADA cross-reactivity assessment data for these patients.

In conclusion, the sponsor did not submit primary data, the method for the cross-reactivity assay or the cut-point on which the sponsor designated the samples as 'negative' for cross reactivity assay data interpretation, therefore, the results cannot be verified. This deficiency was communicated to the sponsor on March 25, 2016. In response, the sponsor submitted additional cross-reactivity analysis data which are reviewed below (see section: [cross reactivity](#)).

FDA comment 2: Please include anti-lixisenatide antibody titers for each of these samples expressed both as a dilution ratio and as the mass units previously provided.

Sponsor's Response: "With the initiation of the phase 3 program the assay format for detection and quantification of anti-lixisenatide antibodies was switched to a Biacore method which provides concentration values in mass units of nmoles/L rather than titers. The radio immune-precipitation method used in earlier phase I/II studies was not utilized. Therefore titers, which are expressed as dilution ratios, are not available for samples in the phase 3 studies, rather the SPR method for calibration-free concentration analysis (CFCA), which provides antibody concentration instead of titer".

Reviewer's comment:

The sponsor stated that the assay format for the detection and quantification of anti-lixisenatide antibodies was switched to a Biacore method, which provides concentration values in mass units of nmoles/L rather than titers. Therefore, they were unable to provide the titer expressed as conventional dilution ratio of the antibodies. In my opinion the response is adequate in the context of the above comment.

FDA comment 3: To better understand the clinical impact of the observed anti-lixisenatide antibodies, in the absence of information regarding the presence of anti-lixisenatide neutralizing antibodies (NAb), please submit an assessment for correlations between PK and PD effects observed with the relative abundance of ADA in lixisenatide-treated subjects.

Sponsor's Response: "The presence of anti-lixisenatide antibodies has a significant effect on the pharmacokinetics of lixisenatide, increasing plasma concentrations to lixisenatide by as much as 10 fold although this effect was highly variable. Because of this, PK/PD and POP PK assessments were conducted in anti-lixisenatide antibody negative subjects and patients based on total lixisenatide concentrations.

As higher total concentrations of lixisenatide in anti-lixisenatide antibody positive patients did not lead to an increase in pharmacodynamics activity of lixisenatide, a cell based potency assay for detection of the activation of the glucagon-like peptide 1 receptor (GLP-1R) by lixisenatide in human plasma samples was established to understand the fraction of total drug that was contributing to activity of lixisenatide in anti-lixisenatide antibody positive and negative patients (DOH0499, Module 2.7.1,

Section 2.1.2.6). This assay had a lower limit of quantitation (LLOQ) of 40 pg/mL compared to the total assay which had a LLOQ of 11 pg/mL. Data from a variety of studies have demonstrated the presence of similar activity in spite of much higher concentration of total drug in anti-lixisenatide antibody positive patients. In pre-dose samples measured at week 24 over a number of studies, mean active concentrations of lixisenatide were approximately 140 pg/ml in measurable samples from anti-lixisenatide antibody negative patients while mean active concentrations ranged from 107 to 132 pg/mL in anti-lixisenatide antibody positive patients (ISE: Module 5.3.5.3 [Table 1.5.3]). The median active fraction ranged from 0.15 to 0.23 in anti-lixisenatide antibody positive patients (ISE: 5.3.5.3 [Table 1.5.5]) over the range of anti-lixisenatide antibody concentrations up to 100 nmol /L (In the highest anti-lixisenatide antibody concentration group (>100 nmol/L) most samples were below the LLOQ for active concentrations). This indicates that in antibody positive patients 15% to 23% of total lixisenatide concentration is not neutralized by the antibodies, and that this extent is not influenced by the antibody concentration <100 nmol/L.

These data demonstrate that while there are substantial differences in total plasma concentrations of lixisenatide between anti-lixisenatide antibody positive and negative patients, the active concentrations of lixisenatide are approximately comparable across the antibody negative and positive groups at least up to anti-lixisenatide antibody concentrations of <100 nmol/L. The similar exposure of active concentrations of lixisenatide in anti-lixisenatide across the antibody negative and positive (with antibody concentration < 100 nmol/L) population correlates well with the similar efficacy observed across these populations (SCE Module 2.7.3 Table 23)."

Reviewer's comment:

The sponsor's response indicates that the presence of anti-lixisenatide antibodies has significantly increased plasma concentrations of lixisenatide and affected pharmacokinetics of lixisenatide. However, the sponsor argued that higher concentrations of lixisenatide in ADA positive patients did not lead to an increase in pharmacodynamics activity of lixisenatide.

Table 2 shows, 78% of patients (n=1475/1890) were either antibody-negative or had an antibody concentration <LLOQ (3.21nmol/L); in these patients the mean change in HbA1c was -0.86% compared with -0.64% in patients with antibody concentration ≥LLOQ and ≤100 nmol/L, whereas 2.4% ADA patients (n=45/1890) had mean change in HbA1c to -16%. Seventeen of these 45 (n=17/45) patients were tested for the cross-reactivity with endogenous GLP-1 and glucagon. According to the sponsor none of these patients showed cross-reactivity of anti-lixisenatide antibodies with endogenous GLP-1 and glucagon. In my opinion, these data cannot be verified since the application package is missing valuable information such as, method validity information, cut point etc. This PK/PD assessment with respect to immunogenicity appears more relevant to the clinical or preclinical reviewer's expertise.

FDA comment 4: If anti-lixisenatide antibodies from your clinical trial samples correlate with observed adverse clinical effects, or demonstrate cross-reactivity with endogenous GLP-1 and/or glucagon, you may be required to test for the presence of NAb using a validated NAb assay. Further, if cross-reactivity with endogenous GLP-1 or glucagon is demonstrated in samples from extended lixisenatide administration (76 weeks or later), the potential for development of a deficiency in one or both of these cross-reactive endogenous targets should be evaluated. Provide a plan to develop a NAb assay in the event that such studies are required.

Sponsor's Response: "Anti-lixisenatide antibody status and concentration had minimal effects on the efficacy and safety of lixisenatide and no cross-reactivity was observed in all subjects that were assessed.

At the end of the main treatment period (24 weeks), the mean change in HbA1c from baseline was similar regardless of antibody status (positive or negative). Almost 80% of patients were either antibody-negative or had an antibody concentration <LLOQ; in these patients the mean change in HbA1c was -0.86% compared with -0.64% in patients with antibody concentration \geq LLOQ and \leq 100 nmol/L. Although patients with antibody concentrations >100 nmol/L had a smaller decrease in HbA1c (-0.16%), analysis of HbA1c change by ADA concentration demonstrated that a high antibody concentration per se is not predictive of diminished efficacy and that antibody concentration cannot predict HbA1c change in an individual patient. There was no imbalance in the incidence of common TEAEs, including GI events, when analyzed by antibody status. During the main treatment period, the percentage of lixisenatide patients with injection site reactions was 5.0% in antibody positive patients and 2.3% in antibody negative patients compared with 1.8% in placebo subjects. Furthermore, no cross-reactivity of anti-lixisenatide antibodies with endogenous GLP-1 and glucagon was observed at the end of the main treatment period (24 weeks). Except in isolated cases, cross-reactivity was not assessed beyond 24 weeks of treatment.

The sponsor developed and validated a NAb assay, based on the induction of cAMP by lixisenatide in cells stably transfected with the human GLP1-Receptor gene. This NAb assay could potentially be employed in case the assessment of the neutralizing capacity of ADAs is deemed necessary".

Reviewer's comment:

The sponsor tested 413 ADA positive subjects at the end of 24 weeks treatment and in some isolated cases (n=18) beyond 24 weeks to evaluate the cross-reactivity of anti-lixisenatide antibodies to endogenous GLP-1 and glucagon. The sponsor determined that none of these subjects were cross-reactive to endogenous GLP-1 or glucagon (the assay cut-points were reestablished later which is discussed below). The sponsor did not submit the validation of cross-reactivity assay or the basis of determining these subjects as

'negative'. This deficiency was communicated to the sponsor on March 25, 2016. In response, the sponsor submitted additional cross-reactivity analysis data which are reviewed below (see section: [cross reactivity](#)). The sponsor stated that they have developed an assay for detection of NAb. The validation and assay SOP for the reported NAb assay will need to be evaluated by the Agency prior to utilization to screen existing study subject samples or samples collected from future studies.

5. Immunogenicity study samples:

5.1 Phase 3 studies:

The immunogenicity assessment was based on anti-lixisenatide antibody data collected in the Phase 3 placebo-controlled study pool (EFC6014, EFC6015, EFC6016, EFC6017, EFC6018, EFC10743, EFC10781, EFC10887, and EFC11321). The study information and protocols for these studies are provided in table 7.

Studies used for immunogenicity assessment:

Table7 – Study information of Phase 3 studies used for immunogenicity assessment

Study Identifier	Study design	Treatment duration	Number of patients evaluated for safety
Phase 3 studies (patients with T2DM) – Placebo-controlled			
EFC6018 GetGoal-Mono	Multinational, randomized, double-blind, placebo-controlled, 4-arm, parallel group study to assess the efficacy and safety of 20 µg QD lixisenatide (2-step or 1-step dose increase) as monotherapy in patients with T2DM	12 weeks	361
EFC6014 GetGoal-M	Multinational, randomized, double-blind, placebo-controlled, 4-arm, parallel-group study to assess the efficacy and safety of 20 µg QD lixisenatide (2-step dose increase) administered morning or evening as an add-on to metformin in patients with T2DM	At least 76 weeks (including the 24-week main treatment period)	680
EFC10743 GetGoal-F1	Multinational, randomized, double-blind, placebo-controlled, 4-arm, parallel-group study to assess the efficacy and safety of 20 µg QD lixisenatide (2-step or 1-step dose increase) as an add-on to metformin in patients with T2DM	At least 76 weeks (including the 24-week main treatment period)	482
EFC6015 GetGoal-S	Multinational, randomized, double-blind, placebo-controlled, 2-arm parallel-group study to assess the efficacy and safety of 20 µg QD lixisenatide (2-step dose increase) as an add-on to SU with or without metformin, in patients with T2DM	At least 76 weeks (including the 24-week main treatment period)	859

EFC6016 GetGoal-L	Multinational, randomized, double-blind, placebo-controlled, 2-arm, parallel-group study to assess the efficacy and safety of 20 µg QD lixisenatide (2-step dose increase) as add-on to basal insulin with or without metformin, in patients with T2DM	At least 76 weeks (including the 24-week main treatment period)	495
EFC10887 GetGoal-L-Asia	Multinational (Asia), randomized, double-blind, placebo-controlled, 2-arm, parallel-group study to assess the efficacy and safety of 20 µg QD lixisenatide (2-step dose increase) as add-on to basal insulin with or without SU in patients with T2DM	24 weeks	311
EFC6017 GetGoal-P	Multinational, randomized, double-blind, placebo-controlled, 2-arm, parallel-group study to assess the efficacy and safety of 20 µg QD lixisenatide (2-step dose increase) as add-on to pioglitazone with or without metformin in patients with T2DM	At least 76 weeks (including the 24-week main treatment period)	484
EFC10781 GetGoal Duo 1	Multinational, randomized, double-blind, placebo-controlled, 2-arm, parallel-group study to assess the efficacy and safety of 20 µg QD lixisenatide (2-step dose increase) as add-on to insulin glargine and metformin (with or without TZD) in patients with T2DM	24 weeks	446
EFC11321 GetGoal-M-Asia	Multinational (Asia), randomized, double-blind, placebo-controlled, 2-arm, parallel-group study to assess the efficacy and safety of 20 µg QD lixisenatide (1-step dose increase) as add-on to metformin with or without SU in patients with T2DM	24 weeks	390

Source: copied from Integrated Summary of safety: AVE0010 – lixisenatide - Version number: 1 06-Jul-2015.

5.2 Antibody status summary in Phase 3 studies:

The anti-lixisenatide antibody assessment data are collected in the Phase 3 placebo-controlled study pool (EFC6014, EFC6015, EFC6016, EFC6017, EFC6018, EFC10743, EFC10781, EFC10887, and EFC11321) which are summarized (organized by study visit) in the following table.

Table 8: Number (%) of patients with positive anti-lixisenatide antibody status by visit in Phase 3 placebo-controlled efficacy/safety studies

Visit	Lixisenatide (N=2869) N/N1 (%)	Placebo (N=1639) N/N1 (%)
Baseline	129/2515 (5.1%)	52/1484 (3.5%)
Week 2	232/2406 (9.6%)	59/1419 (4.2%)
Week 4	879/2354 (37.3%)	67/1409 (4.8%)
Week 12	101/175 (57.7%)	3/93 (3.2%)
Week 24	1370/1968 (69.6%)	103/1318 (7.8%)
Week 76	913/1277 (71.5%)	29/596 (4.9%)
Week 100	226/322 (70.2%)	3/133 (2.3%)

N = the number of patients in the safety population.
N1 = the number of patients with evaluable anti-lixisenatide antibody status in the safety population at the respective visit.
Data Pool 1: EFC6014, EFC6015, EFC6016, EFC6017, EFC6018, EFC10743, EFC10781, EFC10887, and EFC11321.

Source: Integrated Summary of Safety: AVE0010 – lixisenatide - Version number: 1.

Reviewer's comment: *The results provided in the above table indicated that the incidence of ADA positivity by visit was increased from baseline over the first 24 weeks (from 5.1% to 69.6%) and plateaued thereafter, with 71.5% at Week 76 and 70.2% at Week 100 (Table 8) in lixisenatide treated subjects.*

ADA concentration:

The sponsor also measured antibody concentration for all ADA-positive patients but only a small group of ADA-positive patients was included due to insufficient plasma sample volume in the remaining samples. Therefore, these patients were not included in 'antibody evaluable group'.

There were 65 of 2869 lixisenatide patients for whom an evaluable antibody concentration was available at baseline in the Phase 3 placebo-controlled studies, and 59 of these patients (90.8%) had antibodies <LLOQ and 6 patients (9.2%) had antibody concentration \geq LLOQ (Table 9). Number of patients with an evaluable antibody concentration \geq LLOQ increased initially over the first 12 weeks to 59.1% during the study, then returned to 32.4% by Week 24 (34.9% at Week 2, 57.9% at Week 4, and 32.4% at Week 24) and was 44.7% at Week 76.

The number of ADA-positive patients with a measurable antibody concentration \geq LLOQ is increased from week 24 to week 76. At Week 24, out of 1370 ADA-positive patients only 1309 patients had an evaluable antibody concentration, which was <LLOQ for 885 (67.6%) patients and \geq LLOQ for 424 (32.4%) patients (Table 9). Whereas, at Week 76, out of the ADA-positive patients (n=913) only 907 patients had an evaluable antibody concentration, 502 (55.3%) of these patients had antibodies <LLOQ and 405 patients (44.7%) had antibodies \geq LLOQ (Table 9).

In the placebo group, 29 patients had an evaluable antibody concentration, 28 of them were (96.6%) were classified as <LLOQ at baseline and one of them (3.4%) had antibodies \geq LLOQ at baseline. The results indicated that the incidence of patients with an antibody concentration <LLOQ remained stable up to the end of the treatment. The antibody concentration levels of \geq LLOQ appear fluctuated between 0% and 7% of patients over the entire treatment period (Table 9) in placebo group.

Table 9: Summary of anti-lixisenatide antibody positive subjects, stratified by ADA concentration (nmol/L), by visit in Phase 3 placebo-controlled studies

Visit	Placebo (N=1639)	Lixisenatide (N=2869)
Baseline		
Number of patients with evaluable anti-body concentration	29	65
<LLOQ	28 (96.6%)	59 (90.8%)
\geq LLOQ	1 (3.4%)	6 (9.2%)
\leq 100 nmol/L	1 (3.4%)	6 (9.2%)
>100 nmol/L	0	0

Week 2		
Number of patients with evaluable anti-body concentration	36	146
<LLOQ	35 (97.2%)	95 (65.1%)
≥LLOQ	1 (2.8%)	51 (34.9%)
≤100 nmol/L	1 (2.8%)	39 (26.7%)
>100 nmol/L	0	12 (8.2%)
Week 4		
Number of patients with evaluable anti-body concentration	43	717
<LLOQ	40 (93.0%)	302 (42.1%)
≥LLOQ	3 (7.0%)	415 (57.9%)
≤100 nmol/L	3 (7.0%)	355 (49.5%)
>100 nmol/L	0	60 (8.4%)
Week 12		
Number of patients with evaluable anti-body concentration	2	93
<LLOQ	2 (100%)	38 (40.9%)
≥LLOQ	0	55 (59.1%)
≤100 nmol/L	0	53 (57.0%)
>100 nmol/L	0	2 (2.2%)
Week 24		
Number of patients with evaluable anti-body concentration	89	1309
<LLOQ	88 (98.9%)	885 (67.6%)
≥LLOQ	1 (1.1%)	424 (32.4%)
≤100 nmol/L	1 (1.1%)	384 (29.3%)
>100 nmol/L	0	40 (3.1%)
Week 76		
Number of patients with evaluable anti-body concentration	29	907
<LLOQ	27 (93.1%)	502 (55.3%)
≥LLOQ	2 (6.9%)	405 (44.7%)
≤100 nmol/L	2 (6.9%)	365 (40.2%)
>100 nmol/L	0	40 (4.4%)

Week 100

Number of patients with evaluable anti-body concentration	3	230
<LLOQ	3 (100%)	130 (56.5%)
≥LLOQ	0	100 (43.5%)
≤100 nmol/L	0	89 (38.7%)
>100 nmol/L	0	11 (4.8%)

N = the number of patients in the safety population.

Number = the number of patients with antibody assessment.

Lower limit of quantification (LLOQ) = 3.21 nmol/L.

Data Pool 1: EFC6014, EFC6015, EFC6016, EFC6017, EFC6018, EFC10743, EFC10781, EFC10887, and EFC11321.

PGM=PRODOPS/AVE0010/OVERALL/CTD_2015_LIXI/REPORT/PGM/ab_concentratebyvisit_t.sas

OUT=REPORT/OUTPUT/ab_concentratebyvisit_t_p3pc_i.rtf (18JUN2015 - 9:00)

Source: Copied from Integrated Summary of Efficacy: AVE0010 – lixisenatide - Version number: 1.06-Jul-2015.

The sponsor submitted a follow-up study result for the antibody status in a small number of subjects who were reported as ADA-positive at the time of stopping treatment (n=54). The results indicated that the percentage of patients with a positive antibody status decreased over time. Of these, 36/38 (94.7%) of patients were still positive in the first 3 months after treatment discontinuation, 9/14 (64.3%) were still positive after 3 to 6 months, and 3/13 (23.1%) were still positive after 6 months and beyond. Although this study was conducted in a small group of population, it indicates that most ADA-positive patients might be able to reverse their antibody status after the treatment is stopped ([Table 10](#)).

Table 10: Post-treatment anti-lixisenatide antibody status over time in patients with positive antibody status at treatment discontinuation for Phase 3 studies

Time since last dosing	Antibody Status, n/N1 (%)	Lixisenatide antibody positive at treatment discontinuation (N=54)
>28 days - ≤3 months	Positive	36/38 (94.7%)
	Negative	2/38 (5.3%)
>3 months - <6 months	Positive	9/14 (64.3%)
	Negative	5/14 (35.7%)
≥6 months	Positive	3/12 (25.0%)
	Negative	9/12 (75.0%)

N = Number of patient who were antibody positive at treatment discontinuation and who had at least one post-treatment antibody measurement.

N1= number of patient who were positive at the beginning of the interval and who had antibody measurements during the interval.

In case of multiple antibody data within the specified time interval, a patient is defined as anti-lixisenatide antibody positive during the specified time interval if the patient is positive at any time during the respective time interval.

Studies included: EFC6014, EFC6015, EFC6016, EFC6017 and EFC10743.

PGM=PRODOPS/AVE0010/OVERALL/CTD_2015_LIXI/REPORT/PGM/ab_statusdisc_t.sas OUT=REPORT/OUTPUT/ab_statusdisc_t_x.rtf (18JUN2015 - 9:02)

Source: copied from Integrated Summary of Safety: AVE0010 – lixisenatide – Appendix S000: 7-27-2015.

The sponsor assessed potential effect of ADA based on pooled data from 8 pivotal placebo controlled Phase 3 studies (Studies EFC6014, EFC6015, EFC6016, EFC6017, EFC10743, EFC10781, EFC10887 and EFC11321) with a treatment period of at least 24 weeks. The change in HbA1c from baseline to Week 24 by ADA status (positive or negative) and concentration of ADAs was analyzed in the lixisenatide group using a meta-analysis method (weighted average using inverse of variance from each study as weights) based on the pooled data.

ADA status (positive/negative) and a concomitant HbA1c value were available at Week 24 for 1954 lixisenatide-treated patients. The results indicated that 1333 (68.2%) were antibody-positive, and 621 (31.8%) antibody-negative. A small group of patients (45 of 1890; 2.4%) showed a significant change in HbA1c from baseline (-0.83% in antibody-negative patients and -0.16% in antibody-positive patients). In this subgroup of patients (2.4%) had antibody concentration >100 nmol/L ([Table 2](#)). It is not understood at this time if this difference in HbA1c value was a result of the neutralization of the drug product or cross-reactivity of the antibodies with endogenous GLP-1 and glucagon that could abrogate its normal function in glucose metabolism. Additional information was requested from the sponsor to understand the cross-reactivity of antibodies to the endogenous GLP-1 and glucagon.

A similar analysis was performed at Week 76 using long-term pooled data from 5 studies (EFC6014, EFC6015, EFC6016, EFC6017 and EFC10743). At Week 76, ADA status with a concomitant HbA1c value was available for 960 lixisenatide-treated patients, including 656 (68.3%) antibody-positive patients.

The results shown in a table from the submission (review [Table 3](#), above) indicated that a small group of patients (30 of 957; 3.1%) showed a significant change in HbA1c from baseline (-0.96% in antibody-negative patients and -0.52% in antibody-positive patients). In this subgroup of patients (3.1%) had antibody concentration >100 nmol/L.

Reviewer's Comment:

In placebo-controlled Phase 3 studies, the sponsor showed that anti-lixisenatide ADA incidence was increased over the course of treatment in study subjects, and reached an apparent plateau after 24 weeks. After 100 weeks of treatment the overall incidence of anti-lixisenatide ADAs in the trial subjects was approximately 70%. The sponsor also submitted follow-up results of antibody status in 54 subjects who discontinued or stopped the treatment. The results showed that the percentage of patients with a positive antibody status decreased over time. About 95% (n=36/38) of patients were still positive in the first 3 months after treatment discontinuation, 64.3% (9/14) were still positive after 3 to 6 months, and 23.1% (3/13) were still positive after 6 months and beyond. Although these results were generated from a small number of subjects which may need further validation, a trend exists that the percentage of patients with a positive antibody status decreased over time after discontinuation of treatment.

6. Cross reactivity of anti-lixisenatide antibodies with endogenous GLP-1 and glucagon:

The sponsor assessed cross-reactivity of anti-lixisenatide antibodies with endogenous GLP-1 and glucagon in 1269 ADA-positive patients in 3 Phase 3 studies (EFC6015, EFC10781, and EFC11321: [Table 7](#)) using the Biacore T-100 instrument. The sponsor validated an assay for the detection of anti-lixisenatide binding antibodies in human plasma using a SPR method on the Biacore T100. Although the sponsor used SPR T-100 instrument to assess cross-reactivity of anti-lixisenatide antibodies with endogenous GLP-1 and glucagon, this assay was not validated. For validation of this assay, specific positive control antibodies are needed demonstrating that the positive control antibodies are specific, selective, and reproducible in the context for which they are used.

Regarding the cross-reactivity assay the sponsor stated (Ref: sponsor's response on April 22, 2016 pages 3 & 4) that "...within the Biacore assay, flow cell 1 (FC1) serves as control for non-specific binding, whereas flow cells 2, 3 and 4 (FC2, FC3 and FC4) were coated with lixisenatide. % ratios of FC2, FC3 and FC4 are compared to the % ratio of FC1. Lower % ratios of FC2, FC3 and FC4 than % ratio of FC1, are the indicative of cross-reactivity of the peptide with anti-lixisenatide antibodies. Values above 100% ratio are considered as not specific. Briefly, as described in [Supporting Document 02 to DOH0754], for cross-reactivity, the experimental protocol utilized ADA positive samples only that were either unspiked or spiked with GLP-1 or glucagon in large excess (20ug/mL). The % inhibition is then calculated using the relative unit (RU) data obtained for each sample according to the equation $100 \times (1 - \text{spiked RU} / \text{unspiked RU})$. Outliers in the % inhibition data were identified via boxplots using the 3-fold interquartile range (IQR) [$Q3 - 3IQR$; $Q3 + 3IQR$] and are excluded from specificity cut-point calculation". The sponsor stated that they employed a robust parametric method aiming for a 1% false positive rate to calculate the specificity cut-points as described in the draft FDA guideline. Based on this % inhibition data, the sponsor determined specificity cut-points for GLP-1 to be 5.657 % and for glucagon 6.499 %. Using these specificity cut-point the sponsor reported 361 of 1269 (28.4%) subjects were positive for antibodies cross-reacting with GLP-1 and 60 of 1269 (4.7%) patients had ADAs cross-reacting with glucagon.

The initial assessment by the sponsor indicated that none of the samples cross-reacted with endogenous GLP-1 and glucagon. The sponsor arbitrarily chose to use 50% specificity cut-point to determine cross-reactivity for GLP-1 and glucagon. The agency questioned the results because the sponsor did not provide supportive numerical data, only the qualitative classification as either "Positive" or "Negative". Further, this method was not validated. On April 25, 2016, the Agency requested additional information to justify sponsor's claim.

Initial Request:

We acknowledge your March 29, 2016, responses to our request for additional immunogenicity information. You submitted anti-lixisenatide antibody cross-reactivity results to endogenous GLP-1 and native glucagon, which you classified as negative in 212 ADA-positive subjects from three Phase 3 studies (EFC10781, EFC11321 and EFC6015). You did not provide sufficient information for the agency to verify your claim. Provide the following information:

- Submit primary cross-reactivity data for all ADA-positive subjects evaluated for cross-reactivity in these studies. Data should be submitted both in Excel and pdf formats, and should include the ADA level measured for all samples and the timing of sample collection.
- Submit a description of the cross-reactivity method validation and data to demonstrate the suitability of the cross-reactivity method for its intended purpose.

Follow-up to initial request:

Please include the following requests below with your cut-point reevaluation data to be submitted on May 4th, 2016.

- Clarify which Biacore instrument (T100 vs. T200) was used for sample analysis for cross-reactivity of GLP-1 and glucagon.
- Include an additional column in the data table for cross-reactivity results from the new analysis as a percent inhibition of control for each sample.
- Submit data in Excel and pdf formats as previously done.

On May 4th 2016, the sponsor responded that they determined a new specificity cut-point for endogenous GLP-1 and glucagon using samples from three phase 3 studies (EFC6015, EFC10781 and EFC11321) that were negative for ADAs against lixisenatide (509 samples). Response units (RU) from the Biacore T100 instrument were used to calculate % inhibition data according to the equation $100 \times (1 - \text{spiked RU} / \text{unspiked RU})$. Outliers in the % inhibition data were identified via boxplots using the 3-fold interquartile range (IQR) [$Q3 - 3IQR$; $Q3 + 3IQR$]. The sponsor identified 11 outliers for GLP-1 and 16 outliers for glucagon and removed them from the calculation (Response to Agency Request: 04-May-2016). After outlier exclusion both distributions were non-normal, but symmetric ([Fig 4 and Fig 5](#)). A robust parametric method aiming for a 1% false positive rate was employed to calculate the specificity cut-points, as recommended in FDA guidelines.

Cross-reactivity specificity cut-point for GLP-1: 5.657 % inhibition

Cross-reactivity specificity cut-point for Glucagon: 6.499 % inhibition

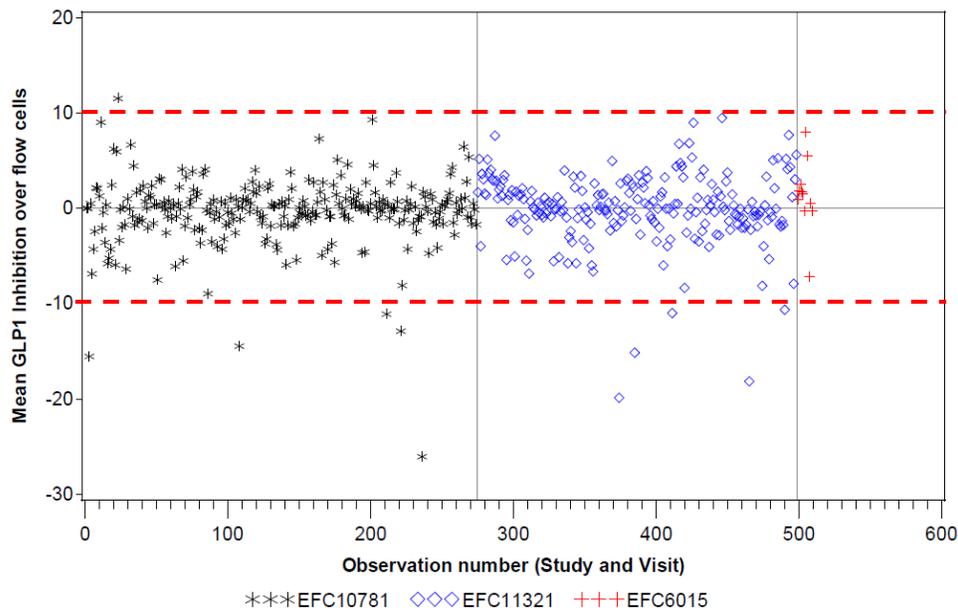
Using the new specificity cut-points, the sponsor determined that anti-lixisenatide antibodies are cross-reactive to 28.4% subjects with endogenous GLP-1 whereas 4.7% subjects are cross-reactive with glucagon.

Reviewer's Comment: *The sponsor plotted percent inhibition data of each sample generated from ADA negative samples of three phase 3 studies (indicated in black, blue and red color) for GLP-1 (Fig 2) and glucagon (Fig 3). Although the sponsor used 1% false positive rate to calculate the specificity cut-point, the final specificity cut-point appears*

very low and closer to background signal. This may indicate a low mean inhibition and low assay variability. Mean inhibition over flow cells for GLP-1 and glucagon were plotted from three studies in the following figures ([Fig 2 and Fig 3](#)). The plot of %inhibition indicates that the results of most of the samples are compacted within a short range of $\pm 10\%$ (Figure 2 and 3: marked by red dotted lines) with few exceptions which could be the outliers. The sponsor removed 11 outliers for GLP-1 and 16 outliers for glucagon from the specificity cut-point calculation. Although this assay is not validated, using the new specificity cut-points, the sponsor determined that anti-lixisenatide antibodies are cross-reactive to endogenous GLP-1 in 28.4% of ADA-positive subjects, whereas 4.7% of subjects have ADA cross-reactive with glucagon.

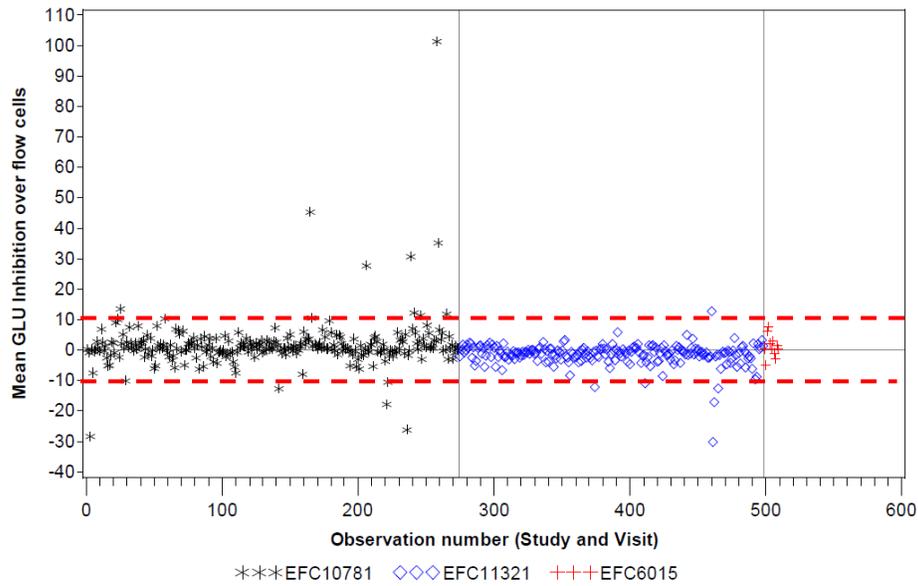
This cross-reactivity assay was not validated using a positive control antibody. In absence of positive control antibodies, the assay specificity or selectivity cannot be justified and can lead to increase in the number of false-positive results, which could undermine the assessment of the relationships between ADA response and clinical safety and efficacy measures. The sponsor should submit a complete cross-reactivity assay validation package for review.

Figure 2: % inhibition data for GLP-1 in the three phase 3 trials (including outliers)



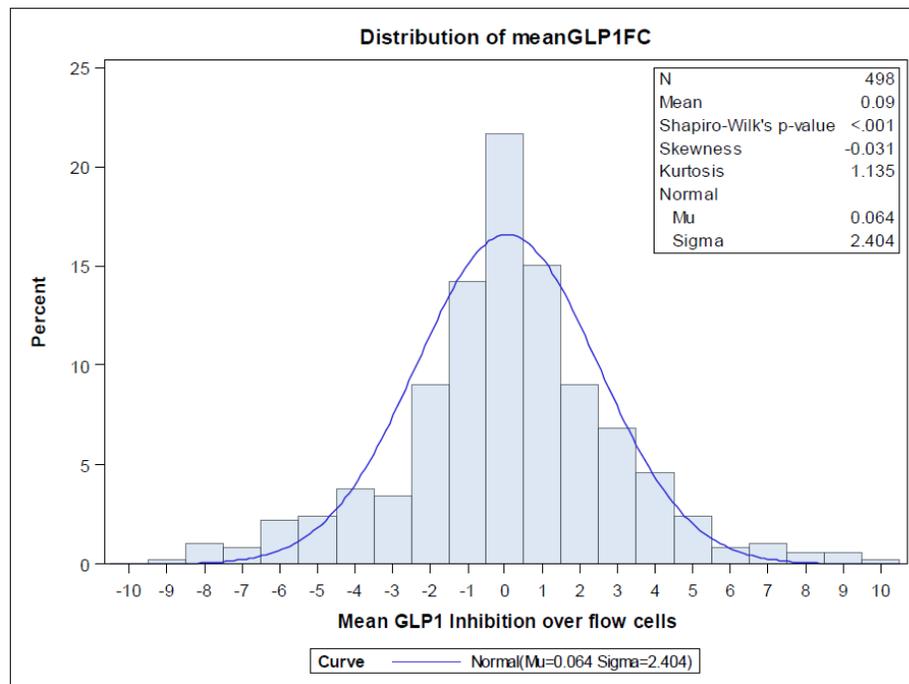
Source: Response to Agency Request: 04-May-2016; NDA 208471 – lixisenatide/AVE0010

Figure 3: % inhibition data for glucagon in the three phase 3 trials (including outliers)

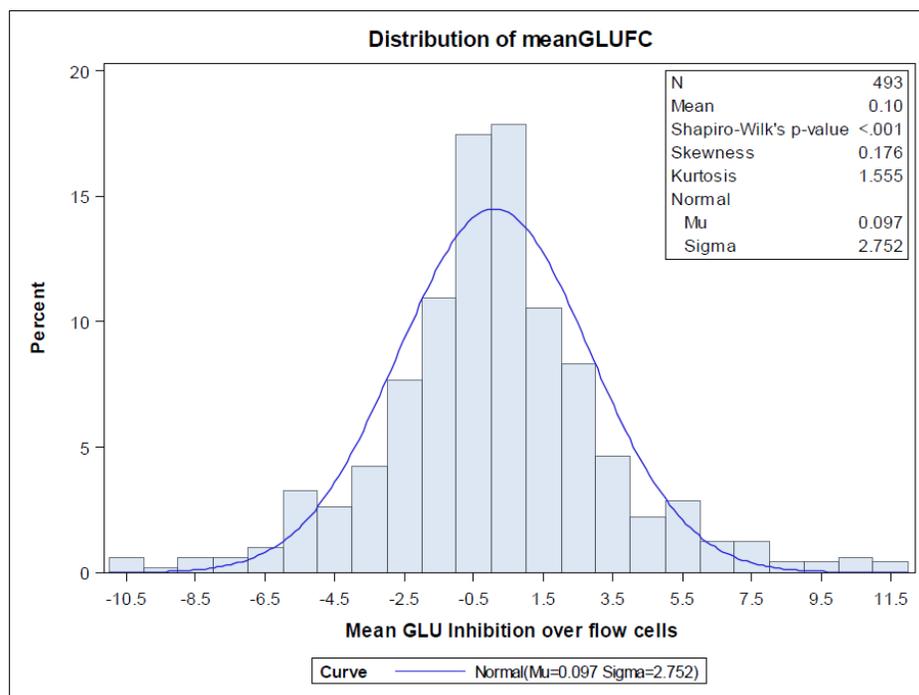


Source: Response to Agency Request: 04-May-2016; NDA 208471 – lixisenatide/AVE0010

Figure 4: Distribution of % inhibition data for GLP-1 (after exclusion of outliers)



Source: Response to Agency Request: 04-May-2016; NDA 208471 – lixisenatide/AVE0010

Figure 5: Distribution of % inhibition data for Glucagon (after exclusion of outliers)

Source: Response to Agency Request: 04-May-2016; NDA 208471 – lixisenatide/AVE0010

Reviewer's Comment:

The figure 4 and figure 5 shows the distribution of % inhibition data for GLP-1 and Glucagon respectively. The distribution data were generated after excluding the outliers. The outliers in the % inhibition data were identified via boxplots using the 3-fold interquartile range (IQR), (data provided in submission but not reproduced in this review). The histograms (Fig 4 and 5) of the % inhibition data without outliers (>3 IQR) are presented above including descriptive statistics, a fitted normal distribution and the result of Shapiro-Wilk test /skewness for normality for GLP1 and glucagon respectively. Based on this data the sponsor used a robust parametric method aiming for a 1% false positive which is good, however, this assay is not validated. The sponsor should submit a complete cross-reactivity assay validation package for review.

7. Summary of Immunogenicity results:

The immunogenicity of lixisenatide in patients with T2DM was assessed by the sponsor. The anti-lixisenatide antibody data collected from nine placebo-controlled Phase 3 studies indicated that the percentage of ADA-positive patients in the lixisenatide group increased with the length of the exposure. The ADA incidence was increased in study subjects over the course of treatment, and reached an apparent plateau of 69.6% by 24 weeks. For those subjects (N) evaluable after 100 weeks of treatment, the overall incidence of anti-lixisenatide ADA remained at 70.2%.

A meta-analysis indicates that the presence of antibodies to lixisenatide may affect the efficacy of the drug since a subgroup of these ADA-positive patients showed a significant change in HbA1c from baseline. In this subgroup (2.4%) the change in HbA1c from baseline (antibody negative or <LLOQ) was -0.86%, compared to -0.16% with antibody concentration >100 nmol/L. This reduced efficacy (HbA1c) may have been due to either; 1) the effect of neutralizing antibodies (NAb) in this population of study subjects or 2) the effect of cross-reaction of the antibodies to the endogenous GLP-1 and glucagon. The sponsor did not assess the clinical samples for neutralizing antibodies; the incidence of cross-reactivity of the antibodies with endogenous GLP-1 was at the rate of 28.4% and with glucagon at a rate of 4.7%. However, the impact of cross-reactive ADA on safety and efficacy of the product is unknown at this time.

IV. REVIEWER CONCLUSIONS:

Immune reactions are frequently observed with peptide products and biologics. Lixisenatide is a non-human synthetic peptide and is highly immunogenic in the T2DM subjects participating in the sponsor's studies. Anti-lixisenatide antibody data were collected from 9 pivotal Phase 3 placebo-controlled studies using a validated binding assay (DARRTS Reference ID: 3373058; September 13, 2013). After 24 weeks, 69.6% of subjects tested positive for lixisenatide ADA, whereas, 71.5% (n=913/1277) patients were ADA positive at week 76. ADA results at week 100 of the study indicate approximately 70.2% (n=226/322) of lixisenatide-treated patients developed antibodies to lixisenatide. These ADA may contain neutralizing antibodies (NAb), because a subgroup of subjects who developed higher concentrations of ADA to lixisenatide at week 24 and week 76 showed reduced efficacies with respect to the evaluation of glycated hemoglobin (HbA1c). No data from NAb testing was submitted by the sponsor. Cross-reactivity of the anti-lixisenatide antibodies with endogenous GLP-1 and glucagon was tested in three placebo-controlled Phase 3 studies, as lixisenatide shows high degree of homology with first 12 amino acid of GLP-1 and glucagon. The cross-reactivity tests results indicated that 28.4% of subjects exhibit ADA cross-reacting with the endogenous GLP-1 and 4.7% of subjects exhibit ADA cross-reacting with glucagon. Sustained treatment with lixisenatide may elicit the formation of neutralizing antibodies to lixisenatide. If expressed, such antibodies may potentially neutralize the normal function of endogenous GLP-1 and glucagon upon binding to them via cross-reactivity, triggering a safety concern for glucose metabolism. The neutralizing antibodies to lixisenatide also could affect the efficacy of the drug product over time.

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06/21/2016

Clinical Inspection Summary

Date	5/12/2016
From	Cynthia F. Kleppinger, M.D., OSI/DCCE/GCPAB Janice Pohlman, M.D., M.P.H., OSI/DCCE/GCPAB, Team Leader Kassa Ayalew, M.D., M.P.H., OSI/DCCE/GCPAB, Branch Chief
To	Suchitra Balakrishnan, M.D., Ph.D., Clinical Reviewer William Chong, M.D., Team Leader Martin White, M.S., Regulatory Health Project Manager Division of Metabolism and Endocrinology Products (DMEP)
Application(s)	NDA 208471
Applicant	Sanofi-Aventis U.S. LLC
Drug	Lixisenatide
NME	Yes
Therapeutic Class	Antidiabetic
Proposed Indication(s)	As an adjunct to diet and exercise to improve glycemic control in the treatment of adults with type 2 diabetes mellitus (T2DM)
Consult Request Date	9/29/2015
Summary Goal Date	6/1/2016
Action Goal Date	7/27/2016
PDUFA Date	7/27/2016

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this NDA consisted of three domestic and two foreign clinical sites. The inspection of one clinical investigator listed below revealed regulatory violations.

In general, based on the inspections of the five clinical sites, the inspectional findings support reliability and/or validity of data as reported by the sponsor under this NDA.

One site, Dr. Min, was issued a Form FDA-483 citing inspectional observations and the preliminary classification is Voluntary Action Indicated (VAI). Although regulatory violations were noted (as described below), they are unlikely to significantly impact primary safety and efficacy analyses. Reliability of data from this site is acceptable for use in support of the indication for this application. The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator.

The classification for Drs. Cerqueira, Dempsey, Howard and Soler is No Action Indicated (NAI). Data from these sites are considered reliable based on the available information. The full

Establishment Inspection Report (EIR) was submitted for review for Drs. Cerqueira, Dempsey and Solar with final classification. The full Establishment Inspection Report (EIR) was not available for review for Dr. Howard. Preliminary inspection results were communicated by the FDA ORA field investigator.

All classifications are considered preliminary until the final communication letter is sent to the inspected entity. An inspection summary addendum will be generated if conclusions change upon receipt and review of the pending EIRs.

II. BACKGROUND

Sanofi-Aventis U.S. LLC has submitted a New Drug Application (NDA) for lixisenatide (AVE0010) as an adjunct to diet and exercise to improve glycemic control in the treatment of adults with type 2 diabetes mellitus (T2DM). Sanofi-Aventis had initially submitted an application December 20, 2012 (under NDA 204961) for lixisenatide. The sponsor withdrew that NDA September 10, 2013 in order to await the complete results of the cardiovascular outcomes study rather than have the FDA review interim data. Previous inspections had been done for studies EFC10743, EFC10781, DRI6012, DRI6014, DRI6018, and DRI6019. There were nine clinical sites and the sponsor inspected under NDA 204961 with no significant findings (See previous CIS finalized October 23, 2013). The consult request for NDA 208471 was readjusted to reduce the number of subsequent sites inspected.

The revised NDA includes the results of three new Phase 3 studies, including a large cardiovascular (CV) outcomes study, one Phase 2 study, and three Phase 1 studies.

Inspections were requested for the following two clinical studies:

- **EFC11319 [ELIXA]**: A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate cardiovascular outcomes during treatment with lixisenatide in type 2 diabetic patients after an Acute Coronary Syndrome event

ELIXA was a double-blind, placebo-controlled, 1:1 randomized, 2-arm, parallel-group, multinational Phase 3 study conducted in adult patients ≥ 30 years of age with type 2 diabetes mellitus (T2DM). Patients had to have been admitted to an acute-care facility for a biomarker-proven, spontaneous Acute Coronary Syndrome (ACS) event: an ST segment elevation myocardial infarction (STEMI) or a non-ST segment elevation myocardial infarction (NSTEMI), or unstable angina within 180 days before screening (as per protocol amendments 2 and 3). The primary efficacy endpoint was time to the first occurrence of any of the following events positively adjudicated by the Cardiovascular Events Adjudication Committee (CAC): CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina.

The ELIXA study began June 24, 2010 and ended February 11, 2015. The study involved 828 sites in 49 countries. There were 7719 subjects screened, 6068 subjects randomized, 6063 subjects treated and 5853 subjects that completed the study.

- **EFC6015:** A randomized, double-blind, placebo-controlled, 2-arm parallel-group, multicenter 24-week study followed by an extension assessing the efficacy and safety of AVE0010 on top of a sulfonylurea in patients with type 2 diabetes not adequately controlled with sulfonylurea

This was a randomized, double-blind, placebo-controlled, 2-arm, unbalanced design, parallel-group study with a 2-step titration regimen (10 µg once daily [QD] for 1 week, then 15 µg QD for 1 week, followed by the maintenance dose of 20 µg QD). The study was double-blind with regard to active and placebo treatments; however, the study drug volume was not blinded. The primary efficacy endpoint was absolute glycosylated hemoglobin (HbA1c) reduction over a period of 24 weeks. There was an initial 24-week treatment period and a variable extension period (at least 76 weeks of treatment).

The study began July 8, 2008 and completed January 14, 2011. The study involved 136 centers in 16 countries. There were 1438 subjects screened, 859 subjects randomized and 600 subjects who completed the study.

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of NDA 208471 in accordance with Compliance Program 7348.811. General instructions were also provided with this assignment.

Sites were chosen based on the OSI site selection tool and no previous inspection history.

For Study EFC11319

- Cerqueira was ranked #1; highest enroller; slightly lower than average discontinuation rate.
- Dempsey was ranked #10; low screening enrollment rate and high discontinuation rate; US site listed as having financial disclosure of speaking fees.
- Howard was ranked # 131; highest US enroller; enrolled 100% screened.

For Study EFC6015

- Min was ranked #2; highest enroller; large treatment effect.
- Soler was ranked #8; larger than average adverse events; low discontinuation rate.

III. RESULTS (by Site):

Name of CI/ Address Site#	Protocol # and # of Subjects Randomized	Inspection Date	Classification
Maria Jose Cerqueira, M.D. Rua Coronel Juca 1952 Fortaleza Ceara 60170-320 Brazil Site 76018	EFC11319 68 subjects	01/18 – 01/29/2016	No Action Indicated (NAI)

Kyung Wan Min, M.D. Eluji General Hospital Endocrinology 280-1 Hagye 1-Dong Nowon-Gu Seoul, n/a 139-872 Korea Site 410510	EFC6015 30 subjects	01/11– 01/15/2016	Voluntary Action Indicated (VAI)*
Michael A. Dempsey, M.D. 3200 Tower Oaks Blvd. Suite 250 Rockville, MD 20852 Site 840430	EFC11319 9 subjects	11/10/2015	No Action Indicated (NAI)
Norman Soler (deceased) 2501 Chatham Road Suite 200 Springfield, IL 62704 Site 840522	EFC6015 11 subjects	12/07 – 12/10/2015	No Action Indicated (NAI)
David Howard 1500E 2nd St., Suite 302 Reno, NV 89502 Site 840382	EFC11319 21 subjects	01/10 – 01/15/2016	No Action Indicated (NAI)*

Key to Classifications

NAI = No deviation from regulations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations; data unreliable.

*Pending = Preliminary classification based on information in 483 (if applicable) and preliminary communication with the field; final classification is pending letter to site.

NOTE: Site inspections focused on 100% review of informed consent documents (ICDs), institutional review board (IRB)/ ethics committee (EC) correspondences, 1572s/investigator agreements, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Source records were compared to the sponsor’s data line listings.

1. Maria Jose Cerqueira/ Site 76018/ Study EFC11319

There were 78 subjects screened and 68 subjects enrolled into the study; 55 subjects completed the study. There were 13 subjects that had early withdrawal. Per the clinical study report, 10 subjects had an adverse event, two subjects were unable to perform study procedures, and one subject withdrew due to the physician’s decision. There were 19 subject records reviewed. The firm worked through the (b) (4) Independent Ethics Committee (IEC) (b) (4) which communicated correspondence for review and approval to a regional IEC Comissao Nacional de Etica em Pesquisa (CONEP).

The site was very organized and there was sufficient oversight of the staff by the clinical investigator. Source documents were compared to the data line listings and they were consistent. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Data from this site appear acceptable.

2. Kyung Wan Min/ Site 410510/ Study EFC6015

There were 45 subjects screened and 30 subjects enrolled into the study; 21 subjects completed the study. Per the clinical study report, five withdrew due to an adverse event, one for lack of efficacy, one was lost to follow-up and two are “other”. There were 10 subject records reviewed; a full review of source visit notes, diaries and case report forms was conducted for the following subjects: 03, 05, 09, 12, 13, 17, 29, 33, 35, 41. The ethics board of record was the Eulji Hospital IRB. All informed consents were translated.

The clinical investigator was very involved with the treatment and evaluation of all subjects. All trainings were documented. The study site had no responsibility for reporting deviations to the IRB or the sponsor at the time of the study. The study protocol did not provide the study site staff with direction on how to report deviations. Deviations were collected by the monitor. The IRB is currently revising their SOPs to require that study sites report deviations with the annual report submission.

There were no unreported adverse events identified. There were no unreported serious adverse events and no deaths experienced by subjects at this site. The primary efficacy endpoint was verifiable.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation. Specifically, not all study related data reported on the electronic case report forms (eCRFs) accurately matches subjects’ source medical history data collected during the study. There were some subject diaries where no medication was recorded as taken but the eCRF stated subject received medication.
 - Subject diary and medical record documented subject #17 did not take study medication on 12/21/2010 and 12/6-17/2010 while CRF states subject received 20µg on these dates. (*Twelve missed days/randomized to active drug*).
 - Subject #41’s diary shows that the study medication was not taken on 12/10/09, 3/27/10, 4/18/10, 6/15-16/10, 6/20/10, 6/29/10, 8/26/10, 8/19/10, 9/20/10,

- 10/27/10, 11/02/10, and 11/24/10; however, the CRF states that study medication was taken on these dates at 20µg. (*Thirteen missed days/randomized to active drug*).
- Subject diary and medical record documented subject #13 did not take study medication on 10/11/2010 while CRF states subject received study medication at 20µg on this date. (*One day missed/randomized to active drug*).
 - Subject diary and medical record documented subject #09 did not take study medication on 10/26-27/2010 but CRF reports that 20µg was taken on these dates. (*Two days missed/randomized to placebo*).
 - Subject #29 lowered study medication dose to 15µg from 4/8-6/7/2010 on 15 different dates but it was reported on the CRF that 20µg was taken on all dates during that time period. (*Randomized to active drug*).

There was also an occasional concomitant medication recorded in the diary but not in the CRF.

OSI Reviewer Comment: A response was sent by Dr. Min on February 4, 2016. He acknowledged study coordinator transcribing errors and has instituted a quality control step to double-check all entries. As the study involved an initial 24-week treatment period (with 168 doses) and a variable extension period (at least 76 weeks of treatment with 532 doses), the missed doses should not have a significant effect on the final analyses.

The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable.

3. Michael Dempsey/ Site 840430/ Study EFC11319

There were 16 subjects screened and nine subjects enrolled into the study; six subjects completed the study. Two subjects were lost to follow-up despite numerous attempts by the site staff to contact them. One subject voluntarily withdrew from the study because he was too busy to make the follow-up visits. Per the clinical study report, five additional subjects could not keep their appointments and two withdrew due to an adverse event. There were nine subject records reviewed [REDACTED] (b) (4). was the IRB of record.

The files were well organized and legible. All training was documented. All subjects met eligibility. Source data matched the data line listings. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Data from this site appear acceptable.

4. Norman Soler/ Site 840430/ Study EFC6015

There were 18 subjects screened and 11 subjects enrolled into the study; 10 subjects completed the study. Per the clinical study report, one subject withdrew for “other” reason. There were 11 subject records reviewed. [REDACTED] (b) (4) was the IRB of record.

The source documents were organized and legible. Records were compared to the data line listings and there were no issues. There was no under-reporting of adverse events and the efficacy endpoints were verifiable.

There was one discussion item at the closeout meeting. Specifically, the protocol (Section 8.2.5) specifies that if the fasting plasma glucose (FPG) or HbA1c are above the threshold values, the investigator should ensure that no reasonable explanation exists for insufficient glucose control (such as intercurrent disease, non-compliance). Where reasonable explanation existed for insufficient glycemic control, the investigator should undertake appropriate action and schedule a FPG / HbA1c assessment at the next visit (in case the next visit is a phone call, it should be replaced by an on-site visit). For three of 11 subjects (001, 007, 016), Dr. Soler determined that alternate explanations for insufficient control existed and failed to conduct a FPG / HbA1c assessment on-site at the next visit. Instead, these subjects were assessed by phone call. No rescue therapy was initiated.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Data from this site appear acceptable.

Dr. Solar passed away in [REDACTED] (b) (6). All correspondences should be sent to: Dr. Frank L. Mikell, Medical Director, HSHS Medical Group Diabetes Research, 1118 Legacy Point Dr., Springfield, IL 62711. Subjects were seen for the study at Springfield Diabetes and Endocrine Center at 2501 Chatham Rd., Springfield, IL 62704 prior to the move to the current location.

5. David Howard/ Site 840382/ Study EFC11319

There were 21 subjects screened and 21 subjects enrolled into the study; 17 subjects completed the study. Per the clinical study report, one subject withdrew due to an adverse event, one subject withdrew for family reasons, one was unable to do the study procedures, and one was unwilling to undergo injections. There were 12 subject records reviewed.

Overall protocol compliance appeared to be adequate. Source documents were compared to data line listings and there were no issues. Protocol deviations that did occur were documented in the study file and reported to the sponsor. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Data from this site appear acceptable.

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Division of Pediatric and Maternal Health Memorandum

Date: March 10, 2016 **Date consulted:** September 10, 2015

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health Team
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health Team
Division of Pediatric and Maternal Health

Lynne P. Yao, MD,
Director, Division of Pediatric and Maternal Health

To: Division of Metabolic and Endocrine Products (DMEP)

Drug: Lixisenatide

NDA: 208471

Applicant: Sanofi-Aventis U.S. LLC

Subject: Pregnancy and Lactation Labeling Recommendations

Indication: As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Class Type: Glucagon-like peptide-1 (GLP-1) receptor agonist

Materials Reviewed:

- DMEP consult request dated September 10, 2015
- Applicant's response to Division's information request of October 8, 2015, dated November 19, 2015
- Lixisenatide Labeling submitted on July 27, 2015

Consult Question:

DMEP requests that DPMH provide comment on the proposed language provided by the Applicant in the labeling in regards to PLLR requirements.

INTRODUCTION

The Division of Metabolic and Endocrine Products (DMEP) consulted the Division of Pediatric and Maternal Health (DPMH) on September 10, 2015, to provide input for appropriate labeling of the pregnancy and lactation subsections of lixisenatide to comply with the Pregnancy and Lactation Labeling Rule format (PLLR). This is a new molecular entity (NME) NDA.

REGULATORY HISTORY

An NDA for lixisenatide was originally submitted on December 20, 2012, but was subsequently withdrawn on September 10, 2013, following discussions with the Agency regarding the proposed process for review of the interim data from the cardiovascular outcomes trial EFC11319. The full study report for the completed ELIXA trial is included in this application.

To further support the proposed labeling in PLLR format, DMEP sent Sanofi an information request on October 8, 2015 requesting:

- A review and summary of all available published literature regarding lixisenatide related to drug use in pregnant and lactating women,
- A review and summary of relevant cases from the Applicant's pharmacovigilance database,
- A revised labeling incorporating the above information that complies with PLLR format to support changes to the Pregnancy and Lactation sections of labeling.

BACKGROUND**Diabetes Mellitus and Pregnancy**

Adverse outcomes of diabetes during pregnancy relate to the onset of diabetes, its duration, and the degree of vasculopathy. Women with pregnancies complicated by diabetes mellitus may be separated into one of two groups:

1. Gestational diabetes (GDM): women with carbohydrate intolerance of variable severity, with onset or first recognition during the present pregnancy. This means that the glucose intolerance may have antedated the pregnancy but was not recognized by the patient or the physician.
2. Pregestational diabetes (PGD): women known to have diabetes before pregnancy.

Ninety percent of all pregnant diabetic women have gestational diabetes mellitus (GDM), whereas type 1 (insulin-dependent diabetes) and type 2 (non-insulin dependent diabetes) account for the remaining 10%.¹

Gestational Diabetes

The incidence of GDM varies in different study populations and is estimated to occur in 3–5% of all pregnant women in the United States. The likelihood of developing GDM is significantly increased among certain subgroups, and these include women with a family history of type 2

¹ Reece, EA, Hobbins, JC: Clinical Obstetrics, Third Edition, Chapter 38: Diabetes Mellitus in Pregnancy, pp: 292-305, Jan 14, 2008

diabetes, advancing maternal age, obesity, and nonwhite ethnicity. Infants born to women diagnosed with GDM do not have an increased risk of congenital anomalies when compared to infants born to women without GDM. GDM usually is diagnosed later in pregnancy when the risk of MCM has passed. PGD that is well under control is not associated with an increased risk either, however, infants of women with poorly controlled PGD have an increased risk of MCM.

Pregestational Diabetes

Poorly controlled PGD during pregnancy increases the risk for maternal complications, including diabetic ketoacidosis, preeclampsia, spontaneous abortions (SAB), preterm delivery, polyhydramnios, stillbirth and cesarean section due to fetal macrosomia. In addition, poorly controlled DM during pregnancy increases the risk for fetal malformations, including neural tube defects (anencephaly, open spina bifida, and holoprosencephaly), cardiovascular anomalies (ventricular septal defects and transposition of the great vessels), oral clefts, genitourinary abnormalities (absent kidneys, polycystic kidney, and double ureter), and sacral agenesis or caudal regression. Fetal complications include pyelonephritis, hypertensive disorders and macrosomia-related injuries (brachial plexus injury, hypoxia). Also directly related to metabolic control are fetal hyperglycemia and neonatal hypoglycemia, hypocalcemia, polycythemia, and hyperbilirubinemia.

Infants of diabetic mothers in unsatisfactory glycemic control often develop hypoglycemia during the first few hours of life. The reported incidence ranges from 25% to 40% of infants of diabetic mothers. Poor glycemic control during pregnancy and high maternal plasma glucose levels at the time of delivery increase the risk of hypoglycemia in the infant. Clinical studies suggest that euglycemia during organogenesis in pregestational pregnant diabetics is critical in the prevention of congenital anomalies.¹ Achieving and maintaining maternal euglycemia prior to conception and throughout pregnancy decreases the risk of adverse outcomes for both the mother and the infant.^{2,3,4}

Poorly controlled pre-gestational Diabetes Mellitus (PGD) (before conception) and in the first trimester is associated with Major Congenital Malformation (MCM) (5-10%) and spontaneous abortion (15-20%).⁵ The higher the fasting serum glucose level is at diagnosis, the higher the incidence of MCM.⁶ The Micromedex database states that pregestational diabetes mellitus in pregnant women with poor control during organogenesis is associated with a 3-fold increase in congenital anomalies that include cardiac malformations, lumbosacral agenesis, hyperbilirubinemia, polycythemia, and renal vein thrombosis. Offspring of mothers with poorly controlled PGD during pregnancy, have a mortality rate that is 5 times greater than that of non-diabetic mothers; the mortality rate is higher at all gestational ages.⁷

² Mills JL. Malformations in infants of diabetic mothers. *Teratology*.1982;25:385-94

³ Persson, M. and Fadi, H. Perinatal outcome in relation to fetal sex in offspring to mothers with pre-gestational and gestational diabetes- a population-based study. *Diabetes Med*. 2014; 31(9): 1047-54.

⁴ www.cdc.gov. Problems of Diabetes in Pregnancy. Accessed 12/30/2015.

⁵ Ornoy, et al. Effect of Maternal Diabetes on the Embryo, Fetus, and Children: Congenital Anomalies, Genetic and Epigenetic Changes and Developmental Outcomes. *Birth Defects Research, Part C: Embryo Today: Reviews*. 2015; 105(1): 53-72.

⁶ Schaefer UM, Songster G, Xiang A, Berkowitz K, Buchanan TA, Kjos SL. Congenital malformations in offspring of women with hyperglycemia first detected during pregnancy. *Am J Obstet Gynecol*. 1997;177:1165–1171.

⁷ The Behrman RE, Kleigman RM, Nelson WE, et al: *Nelson Textbook of Pediatrics*, 14th. WB Saunders Company,

The American College of Obstetricians and Gynecologists (ACOG) in a statement issued in 2005 and reaffirmed in 2012 for PGD, states that HbA_{1c} of 5-6% is associated with a fetal malformation rate close to what is seen in normal pregnancies. A HbA_{1c} near 10% is associated with a fetal anomaly rate of 20-25%.⁸

Drug Characteristics⁹

Lixisenatide is a synthetic analogue of human Glucagon like Peptide-1 (GLP-1) which acts as a GLP-1 receptor agonist to be administered by subcutaneous once daily administration. Other approved GLP-1 receptor agonists in the U.S. include albiglutide & dulaglutide for weekly dosing, exenatide for twice daily & weekly dosing, and liraglutide for daily dosing. All GLP-1 agonists are administered sub-cutaneously. Lixisenatide is a peptide containing 44 amino acids, and is amidated at the C-terminal amino acid (position 44). It is a sterile, clear, colorless aqueous solution for subcutaneous administration. It exerts an incretin effect by stimulating insulin secretion after a meal while inhibiting glucagon secretion, both in a glucose-dependent manner, which limits the risk of hypoglycemia. In addition, it slows down gastric emptying after a meal, which contributes to reduce postprandial hyperglycemia, especially after breakfast.¹⁰ Lixisenatide stimulates glucose dependent insulin secretion by enhancing insulin secretion from pancreatic β -cells among the other modes of action. Lixisenatide has a low level (55%) of binding to human proteins and has a terminal half-life of about 3 hours after multiple dose administration in patients with type 2 diabetes. Nausea and vomiting are the most frequently reported adverse reactions mostly during the first 3 weeks of treatment initiation. Hypoglycemia with severe symptoms has been reported.

Pregnancy and Lactation Labeling Rule

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”¹¹ also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule¹² format to include information about the risks and benefits of using these products during pregnancy and lactation. The PLLR went into effect on June 30, 2015.

Philadelphia, PA, 1992.

⁸ ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists. 2005; 60:675-685.

⁹ Lixisenatide Proposed Labeling. Section 12: Clinical Pharmacology. Submission July 27, 2015.

¹⁰ Scheen AJ. Lixisenatide (Lyxumia), a new agonist of glucagon-like peptide-1 receptors with a predominant postprandial action. *Rev Med Liege*. 2014, Feb; 69(2):102-9

¹¹ *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

¹² *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

LITERATURE REVIEW

Lixisenatide and Pregnancy in Humans

The applicant performed a literature search in Medline and Embase. No relevant publications for pregnancy and lixisenatide were identified for any of the search terms: safety, adverse drug reactions, adverse effects, adverse events, toxicity, drug interactions, embryotoxicity, fetotoxicity, repro-toxicity, genotoxicity. DPMH also conducted a review of PubMed for published literature with similar terms regarding lixisenatide and use in pregnancy, lactation and females of reproductive potential. No relevant articles were identified.

As per (b) (4) data bases, a single case of an infant exposed to lixisenatide during gestation was reported. There were no major congenital malformations identified.

PHARMACOVIGILANCE: APPLICANT'S DATABASE REVIEW

The pharmacovigilance database was searched for solicited and unsolicited cases for patients taking lixisenatide with pregnancy, or exposure via a parent (father). The search included preferred terms in relation to pregnancy, stillbirth, congenital anomalies, spontaneous abortion, ectopic pregnancy, preterm birth, pregnancy and neonatal terms, and exposure via the father. Seven cases were retrieved.

- An Asian 27-year-old female patient had been exposed to approximately 30 days of lixisenatide treatment. She was hospitalized due to oligohydramnios and went in to preterm labor. She delivered a healthy male infant about 40 days before her expected due date (premature).
- A 31-year-old black female became pregnant 2.4 years after the first lixisenatide intake and was advised by her cardiologist, obstetrician and gynecologist to terminate the pregnancy because her heart was not healthy enough to withstand labor. She discontinued the drug and pursued the pregnancy that resulted in a stillbirth.
- A 34-year-old white, Hispanic female who became pregnant 1 year after the first lixisenatide administration. She had a missed abortion at 7.4 weeks gestation followed by dilatation and curettage and stayed in treatment.
- A 54-year-old father on treatment with lixisenatide for over a year who impregnated his partner. The pregnancy resulted in two live births, a boy and a girl born under normal conditions, and with no reported congenital abnormalities.
- A 44-year-old male patient on treatment with lixisenatide for over 2 years who impregnated his wife. She delivered a healthy male-infant vaginally
- Two patients with an event of drug exposure during pregnancy with no adverse events reported and with limited information.

13 (b) (4) data base, (b) (4) Micromedex Solutions, 2016.

No other cases are reported, and the 120 day update report revealed no additional cases of pregnancy.

There is no pregnancy registry for lixisenatide.

Reviewer comment:

The Applicant and DPMH did not identify any new clinical findings related to lixisenatide and use in pregnancy that will be included in the labeling. The reader is referred to Sanofi's "Response to FDA Information Request" of November 19, 2015.

NON-CLINICAL STUDIES^{14,15}

Animal reproduction studies identified increased adverse developmental outcomes from exposure to lixisenatide during pregnancy. Lixisenatide administered to pregnant rats and rabbits during organogenesis was associated with visceral closure defects and skeletal defects at systemic exposures that decreased nutritional intake and weight gain during gestation, and that are 1-time and 4-times higher than the 20 mcg/day clinical dose, respectively, based on plasma AUC. Lixisenatide reduced food intake and weight gain in pregnant rats for just a few days after starting treatment, a transient effect, and yet it resulted in these skeletal and closure defects. At these exposures, the animals experienced concomitant maternal toxicity during these studies. In a second study in pregnant rabbits, no drug-related malformations were observed from twice-daily subcutaneous doses of 0.15 mcg/kg administered during organogenesis, resulting in systemic exposure that is similar to the clinical exposure at 20mcg/day, based on plasma AUC. This 2nd rabbit study was seeking a NOAEL. For further details, the reader is referred to the Pharmacology/Toxicology review by Feleke Eshete, Ph.D.

Reviewer comment:

Glucagon-like peptide-1 (GLP-1) receptor agonists, like lixisenatide, affect appetite and weight. Lixisenatide administration to the pregnant animals, even transiently, causes maternal toxicity defined as poor nutrition that leads to reduced weight gain of the pregnant animals at a critical time of development. The skeletal findings in the pups can be explained by the maternal events. These non-clinical findings without supportive human data or a very clear teratogenic risk (e.g., cytotoxic agents), do not warrant a warnings and precautions statement or use of contraception during treatment with lixisenatide.

As per Applicant, lixisenatide was not mutagenic or clastogenic in a standard battery of genotoxicity tests (bacterial mutagenicity (Ames), human lymphocyte chromosome aberration, mouse bone marrow micronucleus.¹²

Reviewer comment:

The Applicant and DPMH did not identify any new nonclinical findings related to lixisenatide and use in pregnancy that will be included in the labeling. The reader is referred to Sanofi's "Response to FDA Information Request" of November 19, 2015.

¹⁴ Lixisenatide proposed labeling.

¹⁵ Pharmacology/Toxicology review by Feleke Eshete, Ph.D.

Lixisenatide and Lactation

DPMH in review of lixisenatide and lactation including Hale's Medication and Mother's Milk, a breastfeeding expert, identified no records about lixisenatide. A review of Toxnet¹⁶ revealed no records of lixisenatide and lactation. A review of the literature by the Applicant regarding lixisenatide and lactation, failed to produce any publications.

It is not known whether lixisenatide is present in human milk. A study in lactating rats showed low transfer of lixisenatide and its metabolites into milk within 24 hours following a single subcutaneous administration of a 1 mg/kg dose.

Reviewer comment:

Lixisenatide is a peptide and any amount present in human milk would most likely be degraded in the gastrointestinal system (GI) of the infant (as seen in rats). Half-life of lixisenatide is about 3 hours. Therefore, the amount an infant may be exposed to is likely to be low. DPMH recommends that the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for lixisenatide and any potential adverse effects on the breastfed infant from lixisenatide or from the underlying maternal condition.

Lixisenatide and Females and Males of Reproductive Potential

DPMH also conducted a review of published literature in PubMed and Embase to evaluate the use of lixisenatide and its effects on fertility. No records were found. Non-clinical studies in which male and female rats received twice daily subcutaneous doses of 2, 29, or 414 mcg/kg/dose prior to pairing through gestation day 6 did not indicate any adverse effects on male or female fertility in rats up to the highest dose tested, 414 mcg/kg/dose, or approximately 300 times the clinical systemic exposure at 20 mcg/day based on plasma AUC.¹² No adverse effects of GLP-1 agonists on male or female fertility have been observed in animals (mice) even when the drug was administered in very high doses (over 300 times the clinical systemic exposure).

CONCLUSIONS

Lixisenatide labeling has been updated to comply with the PLLR format. A review of the published literature, the Applicant's pharmacovigilance database and other components the NDA submission revealed no new data with lixisenatide use in pregnant or lactating women. DPMH has the following recommendations for lixisenatide labeling:

- **Pregnancy, Section 8.1**
 - The "Pregnancy" subsection of lixisenatide labeling was formatted in the PLLR format to include: "Risk Summary," "Clinical Considerations," and "Data" subsections¹⁷.
- **Lactation, Section 8.2**
 - The "Lactation" subsection of lixisenatide labeling was formatted in the PLLR format to include the "Risk Summary" and "Data."¹⁵

¹⁶ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

¹⁷ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

- **Females and Males of Reproductive Potential, Section 8.3**
 - The “Females and Males of Reproductive Potential” subsection of lixisenatide labeling is omitted because there is nothing to be reported.
- **Patient Counseling Information, Section 17**
 - The “Patient Counseling Information” section of lixisenatide labeling was updated to correspond with changes made to sections 8.1, and 8.2.

RECOMMENDATIONS

DPMH revised sections 8.1, 8.2, and 17 of lixisenatide labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Lixisenatide Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----USE IN SPECIFIC POPULATIONS-----

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data with lixisenatide in pregnant women are not sufficient to inform a drug-associated risk of major birth defects and miscarriage. There are (b) (4) [see *Clinical Considerations*]. (b) (4) from exposure to lixisenatide during pregnancy. Lixisenatide administered to pregnant rats and rabbits during organogenesis was associated with visceral closure and skeletal defects at systemic exposures that decreased (b) (4) intake and weight gain during gestation, and that are 1-time and (4)-times higher than the 20 mcg/day clinical dose, respectively, based on plasma AUC [see *Data*]. (b) (4)

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% in women with a HbA1c >10. The estimated background risk of miscarriage in the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, still birth and delivery complications. Poorly controlled diabetes increases the fetal risk for major (b) (4), still birth, and macrosomia related morbidity.

Data

In pregnant rats receiving twice daily subcutaneous doses of 2.5, 35, or 500 mcg/kg (b) (4) gestation day 6 to 17 (organogenesis), fetuses were present with closure defects (e.g., microphthalmia, bilateral anophthalmia, diaphragmatic hernia) and stunted growth. Impaired ossification associated with skeletal malformations (e.g., bent limbs, scapula, clavicle, and pelvis) were observed at \geq (b) (4) 5 mcg/kg/dose, resulting in systemic exposures that (b) (4) 1 time the 20mcg/d clinical dose, based on plasma AUC. Decreases in maternal body weight, food consumption, and motor activity were observed concurrent with the adverse fetal findings. Placental transfer of lixisenatide to developing rat fetuses is low with a concentration ratio in fetal/maternal plasma of 0.1%.

In pregnant rabbits receiving twice daily subcutaneous doses of 2.5, 25, 250 mcg/kg (b) (4) gestation day 6 to 18 (organogenesis), fetuses were present with multiple visceral and skeletal malformations, including closure defects, at \geq (b) (4) 5 mcg/kg/dose or systemic exposures that are (b) (4)

times the 20 mcg/day clinical dose, based on plasma AUC. Decreases in maternal body weight, food consumption, and motor activity were observed concurrent with the fetal findings. Placental transfer of lixisenatide to developing rabbit fetuses is low with a concentration ratio in fetal/maternal plasma of $\leq 0.0004\%$. In a second study in pregnant rabbits, no drug-related malformations were observed from twice daily subcutaneous doses of 0.15 mcg/kg administered during organogenesis, resulting in systemic exposure $(b)(4)$ the clinical exposure at 20mcg/day, based on plasma AUC.

In pregnant rats given twice daily subcutaneous doses of 2, 20, or 200 mcg/kg from gestation day 6 through lactation, decreases in maternal body weight, food consumption, motor activity were observed at all doses. Skeletal malformations and increased pup mortality were observed at $(b)(4)$ 0 mcg/kg/dose, which is approximately 200-times the 20 mcg/day clinical dose, based on mg/m^2 .

8.2 Lactation

Risk Summary

There is no information regarding the presence of $(b)(4)$ in human milk, the effects on the breastfed infant, or the effects on milk production. However, lixisenatide is present in rat milk [see Data]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for lixisenatide and any potential adverse effects on the breastfed infant from lixisenatide or from the underlying maternal condition.

Data

A study in lactating rats showed low (9.4%) transfer of lixisenatide and its metabolites into milk and negligible (0.01%) levels of unchanged lixisenatide peptide in the gastric contents of weaning offspring. $(b)(4)$

17 Patient Counseling Information

Use in Pregnancy: Advise patients to inform their physicians if they are pregnant or intend to become pregnant

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/s/

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04/04/2016

TAMARA N JOHNSON
04/06/2016

LYNNE P YAO
04/07/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)**

Epidemiology: Review of Study Report

Date: April 7, 2016

Reviewer: Christian Hampp, PhD
Division of Epidemiology I

Team Leader: Patricia L. Bright, MSPH, PhD
Division of Epidemiology I

Associate Division Director: Simone Pinheiro, ScD, MSc
Division of Epidemiology I

Subject: Review of sponsor's comparison of anaphylaxis and hypersensitivity event rates among patients exposed to lixisenatide in clinical trials to rates from an external population

Drug Name: Lixisenatide

Application Type/Number: NDA 208471

Submission Numbers: 16, 21, 24

Applicant/sponsor: Sanofi

OSE RCM #: 2016-641

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EXECUTIVE SUMMARY

This DEPI-I review provides a critical evaluation of the sponsor's analysis comparing anaphylaxis and hypersensitivity event rates from clinical trials of lixisenatide with event rates among users of other glucagonlike peptide-1 (GLP-1) analogs and among type 2 diabetic patients using administrative claims data. This review can assist the Division of Metabolism and Endocrinology Products (DMEP) and the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) in understanding findings and limitations of the sponsor's analysis.

The sponsor conducted two separate analyses, including comparisons of incidence rates of anaphylaxis and hypersensitivity among subjects exposed to lixisenatide in clinical trials (1) to age- and sex standardized rates among patients exposed to exenatide, liraglutide, albiglutide, or dulaglutide, based on (b) (4) administrative claims data, and (2) to age- and sex standardized rates in a type-2 diabetic population, also based on administrative claims data.

In crude analyses incidence rates of anaphylaxis with exenatide (0.06/100 person-years, PY) and liraglutide (0.08/100 PY) based on claims data were comparable to rates of anaphylaxis among patients randomized to lixisenatide in the clinical trials (0.07/ 100 PY). Incidence rates of hypersensitivity for exenatide ((b) (4)/100 PY) and liraglutide ((b) (4)/100 PY) in the (b) (4) database were higher than incidence rates for lixisenatide ((b) (4)/100 PY) in the clinical trials.

In age- and sex- standardized analyses, the investigators found that counts of anaphylaxis events observed among clinical trial subjects randomized to lixisenatide were similar to counts expected in other GLP-1 analog initiators as a reference population (Standardized incidence ratio [SIR] = 1.10; 95% CI, 0.55 - 2.20). Compared to a general type-2 diabetic population, counts of anaphylaxis events observed among clinical trial subjects randomized to lixisenatide were higher than expected counts: SIR = 1.45 (95% CI, 0.73 - 2.90), albeit not statistically significant. However, anaphylaxis events among clinical trial controls and hypersensitivity reactions among lixisenatide subjects and controls in clinical trials were less common than expected based on comparisons with GLP-1 analog initiators or with type-2 diabetic patients in (b) (4) data, with SIRs ranging from (b) (4).

DEPI-I staff identified potential biases that may (1) favor lixisenatide, (2) not favor lixisenatide, and (3) for which data are insufficient to determine directionality of bias. Due to the limitations outlined in this review, results of incidence rate comparisons between clinical trials and administrative claims data should be interpreted with great caution. These analyses are not able to inform causality and they were not conducted for that reason. At most, these analyses can help understand differences between the clinical trial populations and diabetic patients, including GLP-1 analog users, in clinical practice with regard to anaphylaxis and hypersensitivity. However, even these comparisons are limited by the presence of potential biases. The most valid inferences are those made within the clinical trials, based on randomized treatment.

1 INTRODUCTION

This DEPI-I review provides a critical evaluation of the sponsor’s analysis comparing anaphylaxis and hypersensitivity event rates from clinical trials of lixisenatide with event rates among users of other GLP-1 analogs and among type-2 diabetic patients using administrative claims data. This review can assist DMEP and the EMDAC in understanding findings and limitations of the sponsor’s analysis.

On July 27, 2015, Sanofi submitted NDA 208471 for lixisenatide, a GLP-1 analog, as an adjunct to diet and exercise to improve glycemic control in the treatment of adults with type 2 diabetes mellitus. An NDA (NDA 204961) for lixisenatide was originally submitted to the FDA on December 20, 2012, but was subsequently withdrawn by the applicant. Lixisenatide was first approved in Mexico on January 7, 2013, and is currently approved in over 60 countries, including member states of the European Union.

The Division of Metabolism and Endocrinology Products has identified anaphylaxis and hypersensitivity reactions as significant clinical issues. Concerns about these events were based on an imbalance in clinical trials not favoring lixisenatide (16 vs. 5 anaphylaxis events) and 47 postmarketing cases of hypersensitivity reactions associated with lixisenatide from the Sanofi global pharmacovigilance database.

On February 26, 2016, the sponsor submitted a document (“White Paper”) titled “Evaluation of hypersensitivity in the lixisenatide development program,” dated the same day. On March 17 and March 21, 2016, FDA requested additional information from the sponsor, which the sponsor provided on March 28, 2016. The sponsor’s response also included study protocols for the analyses at hand. On March 30, 2016, FDA requested further detail not included in the sponsor’s previous response. The sponsor provided the missing information on April 1, 2016.

2 REVIEW METHODS AND MATERIALS

This review was based on the sponsor’s White Paper, especially Section 3.2.2, titled “Incidence in a reference population.” In addition, DEPI-I staff reviewed the sponsor’s subsequent responses to FDA’s information requests, including the two study protocols.

3 REVIEW RESULTS

3.1 SCOPE OF STUDY

The sponsor conducted two separate analyses. The first analysis included comparisons of incidence rates of anaphylaxis and hypersensitivity among patients exposed to lixisenatide in clinical trials to rates among patients exposed to exenatide, liraglutide, albiglutide, and dulaglutide, based on administrative claims data. The second analysis compared incidence rates of anaphylaxis and hypersensitivity among patients exposed to lixisenatide in clinical trials to rates from a type-2 diabetic population, based on administrative claims data.

3.2 STUDY METHODS

3.2.1 Study Type

Cohort study comparing clinical trial incidence rates with external, administrative claims-based comparator.

3.2.2 Time Period

3.2.2.1 Lixisenatide Clinical Trials

The 20 Phase 2/3 clinical trials were conducted between 2006 and 2015, with varying start and completion dates.

3.2.2.2 (b) (4) Database

In their first analysis, the investigators established cohorts of users of exenatide, liraglutide, albiglutide, and dulaglutide. The start of the study period in the (b) (4) database depended on market availability of each drug and ranged from January 1, 2007 (exenatide), to September 19, 2014 (dulaglutide). The study period ended for all drugs on March 31, 2015.

The study period in the second analysis —comparison with type-2 diabetic patients— ranged from January 2007 through March 2015.

3.2.3 Population and Exposure

3.2.3.1 Lixisenatide Clinical Trials

The analyses included patients who were part of the Phase 2/3 safety population: 20 clinical trials including 18 controlled (13 placebo, 5 active) and 2 lixisenatide only studies.

3.2.3.2 (b) (4) Database¹

The first analysis included patients with new exposure to exenatide, liraglutide, albiglutide, or dulaglutide. Type-2 diabetic patients² were included if they had a prescription for a GLP-1 analog drug preceded by at least 180 days of continuous eligibility without receipt of a GLP-1 analog drug and without a diagnosis for the outcome of interest. The investigators allowed for a gap of up to 30 days to define episodes of GLP-1 analog exposure. The risk window began with initiation of a study

¹ Sponsor-provided database description: The (b) (4) claims databases contain healthcare data - enrollment, inpatient, outpatient, and drug data on more than 230 million unique patients since 1995. The (b) (4) Database, which includes employer and health-plan sourced healthcare data on an employed population and their families, averages more than 49 million unique patients per year in the last three years. The Medicare Supplemental Database, which captures Medicare-eligible retirees with employer sponsored Medicare Supplemental plans, averages over 4 million unique patients per year in the last three years.

² With ICD-9-CM codes 250.x or 250.x2 in baseline period

drug and ended with earliest of: outcome of interest, end of drug supply, end of database eligibility, or March 31, 2015.

The second analysis included type-2 diabetic patients³ 18 years or older who were continuously enrolled in the (b) (4) database for at least 6 months between January 2007 and March 2015 prior to the index date. Patients were followed from the date of their second type-2 diabetes code until the earliest of: outcome of interest, end of database eligibility, or March 31, 2015.

3.2.4 Outcome

3.2.4.1 Lixisenatide Clinical Trials

The investigators included cases of anaphylaxis and hypersensitivity based on a MedDRA SMQ search of the site investigators' verbatim term, instead of an analysis of events adjudicated by the Allergic Reaction Adjudication Committee (ARAC). Of note, hypersensitivity reactions in these analyses were identified using an algorithm to detect angioedema. Terms included in the MedDRA search algorithms are listed in the Appendix.

3.2.4.2 (b) (4) Database

Anaphylaxis and hypersensitivity events were defined through the presence of at least one of the following ICD-9-CM diagnosis codes in inpatient, outpatient, and emergency department visits in the (b) (4) database.

Anaphylaxis:

- 1) 995.0 (anaphylaxis)
- 2) 999.49 (anaphylactic reaction due to other serum)

Hypersensitivity reactions (angioedema):

- 1) 995.3 (allergy, unspecified not elsewhere classified)
- 2) 995.1 (angioneurotic edema not elsewhere classified)
- 3) 995.27 (other drug allergy)
- 4) 374.82 (edema of eyelid)
- 5) 376.33 (orbital edema or congestion)
- 6) 478.25 (edema of pharynx or nasopharynx)
- 7) 478.6 (edema of larynx)
- 8) 708.0 (allergic urticaria)
- 9) 708.8 (other specified urticaria)
- 10) 708.9 (urticaria unspecified)

³ With ≥ 2 ICD-9-CM codes 250.x and 250.x2, separated by at least 30 days

In its March 28, 2016, response to FDA's information request, the sponsor noted that information on the sensitivity for the two coding algorithms was not available. The sponsor provided a reference (1) that found a positive predictive value (PPV) of (b) (4) % ((b) (4)) when ICD-9-CM codes 995.0 and 999.4 were used to identify anaphylaxis in inpatient or emergency department encounter. According to the sponsor, the PPV of the algorithm to identify hypersensitivity reactions was not available.

3.2.5 Statistical Analyses

3.2.5.1 Comparison with Other GLP-1 Analog Drugs

In the first analysis, the investigators compared crude incidence rates for anaphylaxis and hypersensitivity among lixisenatide-exposed clinical trial subjects with incidence rates observed among initiators of other GLP-1 analogs drugs in the (b) (4) database. In the March 28, 2016, response to FDA's request for information, the sponsor also described analysis of SIRs, from a comparison of the number of observed cases of anaphylaxis and hypersensitivity reactions in the lixisenatide clinical trials with the expected number of cases based on age- and sex- specific incidence rates among other GLP-1 analog drug initiators in the (b) (4) database as a reference population.

3.2.5.2 Comparison with Type-2 Diabetic Population

In the second analysis, the investigators calculated SIRs to compare the number of observed cases of anaphylaxis and hypersensitivity reaction in the lixisenatide clinical trials with the expected number of cases based on age- and sex- specific incidence rates from a type-2 diabetic reference population in the (b) (4) database.

In both analyses, the investigators calculated expected event counts by multiplying age-⁴ and sex-specific incidence rates in the reference population by the person-years in corresponding age/sex groups in each treatment arm in the clinical trials, and summing up the products in all age/sex groups.

3.3 STUDY RESULTS

3.3.1 Comparison with Other GLP-1 Analog Drugs

Tables 1-3 provide anaphylaxis and hypersensitivity rates observed in lixisenatide clinical trials (7,874 lixisenatide patients and 6,069 placebo/control patients) and among users of GLP-1 analog drugs in the (b) (4) database.

The investigators found that rates of anaphylaxis with exenatide ((b) (4) /100 PY, Table 2) and liraglutide ((b) (4) /100 PY) were (b) (4) to rates of anaphylaxis among patients randomized to lixisenatide in the clinical trials (0.07/ 100 PY, Table 1). Incidence rates

⁴ Age categories: 18-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, 85+ years.

for albiglutide and dulaglutide may not be reliable because they were based on very few events.

Incidence rates of hypersensitivity for exenatide (^{(b) (4)}/100 PY, Table 3) and liraglutide (^{(b) (4)} 100 PY) in the ^{(b) (4)} database were ^{(b) (4)} incidence rates for lixisenatide (0.58/100 PY, Table 1) in the clinical trials.

Table 1. Incidence of anaphylaxis and hypersensitivity: lixisenatide clinical trials (Table 4 in first response to IR)

Outcome	Lixisenatide (N=7874)			Placebo/Control (N=6079)		
	Person-years (PYs)	# of Events	Incidence rate (per 100 PY; 95% CI)	Person-years (PYs)	# of Events	Incidence rate (per 100 PY; 95% CI)
Anaphylaxis	11276	8	0.07 (0.02-0.12)	9288	2	0.02 (0-0.05)
Hypersensitivity	11207	65	0.58 (0.44-0.72)	9229	50	0.54 (0.39-0.69)

Table 2. Incidence of anaphylaxis associated with marketed GLP-1 agonists: ^{(b) (4)} database (Table 5 in first response to IR)

Generic Drug Name	# of Patients	Person-Years	# of events	Incidence Rate (per 100 PY; 95% Confidence Interval)
Exenatide	107479	52003	^{(b) (4)}	^{(b) (4)}
Liraglutide	118343	64863		
Albiglutide	1627	276		
Dulaglutide	1699	186		
Combined GLP-1 Agonists	229239	123327		

Table 3. Incidence of hypersensitivity associated with marketed GLP-1 agonists: ^{(b) (4)} database (Table 6 in first response to IR)

Generic Drug Name	# of Patients	Person-Years	# of events	Incidence Rate (per 100 PY; 95% Confidence Interval)
Exenatide	106373	56862	^{(b) (4)}	^{(b) (4)}
Liraglutide	117162	63569		
Albiglutide	1615	274		
Dulaglutide	1677	183		
Combined GLP-1 Agonists	226827	120888		

Table 4 shows results of the age- and sex- standardized SIR analyses with other GLP-1 analog initiators (combined) in ^{(b) (4)} data as a reference population. Counts of anaphylaxis events observed among clinical trial participants randomized to lixisenatide

were similar to those expected in other GLP-1 analog initiators: SIR = (b) (4) (b) (4)). However, anaphylaxis events among clinical trial controls and hypersensitivity reactions among lixisenatide subjects and controls in clinical trials were (b) (4) expected based on (b) (4) data. Of note, the sponsor characterized the risk of anaphylaxis in the clinical trial controls as “comparable” to patients treated with other GLP-1 receptor agonists (SIR = 0.34, 95% CI: 0.09 – 1.37).

Table 4. Age- and sex-adjusted standardized incidence ratios (SIR): patients treated with other GLP-1 receptor agonists as the reference population (Table 2 in first response to IR)

Outcome	Lixisenatide			Placebo/Control		
	Observed Number of Events	Expected Number of Events	SIR (95% CI)	Observed Number of Events	Expected Number of Events	SIR (95% CI)
Anaphylaxis	8	7.27	1.10 (0.55-2.20)	2	5.83	0.34 (0.09-1.37)
Hypersensitivity reactions	65	170.58	0.38 (0.30-0.49)	50	135.81	0.37 (0.28-0.49)

3.3.2 Comparison with Type-2 Diabetic Population

Table 5 shows results of the age- and sex- standardized SIR analyses with type-2 diabetic patients in (b) (4) data as reference population. Counts of anaphylaxis events observed clinical trial subjects randomized to lixisenatide were (b) (4) expected counts in type-2 diabetic patients: SIR = (b) (4), albeit not statistically significant. Of note, the sponsor characterized this SIR as “comparable.” At the same time, observed counts of anaphylaxis among clinical trials controls were lower than expected counts in type-2 diabetic patients: SIR = 0.45 (95% CI, 0.11-1.81).

Table 5. SIRs for anaphylaxis observed in lixisenatide clinical trials (Table 5 in original study report).

Treatment	Observed in Clinical Trials	Expected Based on (b) (4) Data*	SIR (95%CI)
Lixisenatide treated	8	(b) (4)	1.45 (0.73-2.90)
Controls	2	(b) (4)	0.45 (0.11-1.81)

*this analysis was performed using the US (b) (4) database. Numbers of observed events in clinical trials derived from SMQ analysis of hypersensitivity and anaphylactic reactions.

Fewer events of hypersensitivity reaction were observed in the clinical trials (regardless of exposure to lixisenatide or comparator) than would be expected in an age- and sex-matched type-2 diabetic population (Table 6).

Table 6. SIRs for hypersensitivity reactions observed in lixisenatide clinical trials (Table 6 in original study report).

Treatment	Observed in Clinical Trials	Expected Based on MarketScan® Data ^a	SIR (95%CI)
Lixisenatide treated	65	(b) (4)	0.43 (0.34 – 0.55)
Controls	50	(b) (4)	0.41 (0.31- 0.54)

^athis analysis was performed using the US (b) (4) database. Numbers of observed events in clinical trials derived from SMQ analysis of hypersensitivity and anaphylactic reactions.

3.4 STUDY CONCLUSIONS

The investigators concluded that results of the SIR analyses indicated that the number of anaphylaxis events observed in lixisenatide treated subjects was (b) (4) to that expected in patients with type-2 diabetes in the (b) (4) database. The number of anaphylaxis events observed among clinical trial controls, however, tended to be (b) (4) than expected counts among type-2 diabetic patients in the (b) (4) database.

For hypersensitivity reactions, the number of events observed in lixisenatide treated clinical trial subjects was (b) (4) than expected counts among patients with type-2 diabetes in the (b) (4) database. Similar results were found for clinical trial controls.

4 DISCUSSION

The sponsor conducted these analyses to provide additional context to the imbalances in anaphylaxis observed in clinical trials and hypersensitivity events reported post-marketing. Because the worldwide cumulative patient exposure to lixisenatide is small (~61,000 person-years in 60 countries, as of September 30, 2015), the sponsor's options for further analysis were limited. However, although a comparison between observed clinical trial event rates with those expected in an age- and sex-matched external population can be useful, their interpretability is limited in this case.

The sponsor's analyses found that rates of anaphylaxis among lixisenatide-exposed clinical trial subjects were as high, or higher, than expected in an age- and sex-matched external population (GLP-1 analog exposed or type-2 diabetic). Rates for anaphylaxis among clinical trial controls and rates for hypersensitivity reaction among lixisenatide subjects and controls in clinical trials were lower than expected in an external population (GLP-1 analog exposed or type-2 diabetic). I disagree with the sponsor's characterization of the SIR for anaphylaxis between lixisenatide-exposed clinical trial subjects and type-2 diabetic controls (SIR = 1.45; 95% CI, 0.73-2.90) as "comparable."

Similarly, the risk of anaphylaxis in clinical trial controls was considered “comparable” to the risk in patients treated with other GLP-1 receptor agonists (SIR = 0.34, 95% CI: 0.09 – 1.37). The investigators may have based these characterizations purely on the absence of statistical significance, yet both a 1.45 ratio and a 0.34 ratio between observed and expected events appear clinically meaningful and should therefore not be described as “comparable.”

Several important biases need to be considered when interpreting these data. The following section includes a description of biases, categorized according to their potential to result in lower (favoring lixisenatide/clinical trials) or higher (not favoring lixisenatide/clinical trials) rates of hypersensitivity reactions or anaphylaxis in clinical trials compared with (b) (4) data. Biases for which existing data are insufficient to inform a likely directionality are included in a third category.

1. Biases favoring lixisenatide/clinical trials

- a. **Use of drug samples may have resulted in underestimated event rates among comparator drug users.** Comparator drugs (other GLP-1 analogs) are often initiated with samples dispensed in a physician’s office, which are not apparent in pharmacy claims data. For instance, between 2009 and 2013, 38.1% of newly initiated exenatide was through a sample (2). Anaphylaxis and hypersensitivity events that occur during periods of sample use in these analyses would therefore not be attributed to the comparator drugs. In addition, patients who experienced these events during periods of sample use may not continue to use the drug (depletion of susceptibles). As a consequence, cohorts based on patients who fill a prescription in a pharmacy (some of whom after using a sample of the same drug without experiencing adverse events) may be less susceptible to these events compared with true new user cohorts in the clinical trials.
- b. **Longer average follow-up in clinical trials compared with (b) (4) could have resulted in lower clinical trial rates for events that occur early after treatment initiation.** Average follow-up of GLP-1 analog drug users was only approximately 0.5 years, while clinical trials subjects were exposed to lixisenatide or comparator for an average of approximately 1.3 years. A listing of adjudicated anaphylactic events indicates that latency was often short, with 8 out of 10 events occurring within 30 days of treatment initiation (White Paper, Section 7.2; Note: these events differ somewhat from the 8 SMQ events included in the analyses at hand). If events of interest tend to occur early after treatment initiation, cohorts with shorter average follow-up time will include proportionately more time at higher risk. Longer average follow-up times in the clinical trials may therefore have introduced bias in favor of lixisenatide.
- c. **The use of MedDRA SMQ (narrow) search to ascertain events in clinical trials may have yielded fewer events than alternative methods of ascertainment.** The sponsor justified this choice (rather than using adjudicated cases) by explaining that the use of the investigator reported terms would be more likely to mirror the terminology collected in the claims database, which is not subject to an adjudication process. Although this explanation has merit, users of these data should be aware that this choice resulted in fewer events as compared

to alternative approaches. For instance, the SMQ-based analysis included 8 anaphylaxis events among clinical trial subjects exposed to lixisenatide, but 16 events were identified by ARAC who adjudicated 10 events as related to investigational drug.

2. Bias **not favoring lixisenatide/clinical trials**

a. **Detection bias could have resulted from underascertainment of non-severe anaphylaxis or hypersensitivity events in claims data (e.g. urticaria).** These and similar non-severe events that may not have been brought to a provider's attention in clinical practice. However, regularly scheduled follow-up visits and standardized patient assessment may have resulted in more complete ascertainment of these events in clinical trials of lixisenatide, resulting in a biased comparison not favoring lixisenatide/clinical trials.

3. Biases for which existing **data are insufficient** to support a prediction of likely directionality

a. **Comparability between algorithms used to identify anaphylaxis and hypersensitivity in clinical trials vs. claims data is unclear.** Due to differences in available data, the investigators had to apply different algorithms to ascertain events of interest in clinical trials (based on SMQ, Appendix) vs. claims data (based on ICD-9-CM codes, Section 3.2.4.2). Differences between these algorithms are noteworthy. For instance, as part of the hypersensitivity algorithm, it is not clear whether "allergic edema" (SMQ, used in clinical trials) would yield equivalent cases as ICD-9-CM code 995.3 (allergy, unspecified not elsewhere classified). Ultimately, we are not able to determine whether these algorithms are equivalent.

b. **Limited PPV and sensitivity could have biased incidence rate estimates.** Even if the algorithms were designed to ascertain the same events (See item 3.a, above), differences in sensitivity and PPV could have introduced bias. The sponsor was not able to provide sensitivity for the ICD-9-CM coding algorithms used in this study. As discussed in Section 2.a, above, sensitivity may be reduced for events of lower severity, resulting in underascertainment. However, limited PPV may have had an opposite effect. The sponsor provided a reference (1) that found a positive predictive value (PPV) of 69.0% (95% CI, 58.0 - 78.7%) for anaphylaxis based on inpatient or emergency department encounters. However, the sponsor ascertained these events in all types of patient encounter, including outpatient visits. As the authors of the validation study noted: "outpatient encounters generally have lower PPVs." Thus, the algorithm as used by the sponsor arguably suffers from even lower PPV. Reduced PPV results from the inclusion of false-positives, thus inflating the observed event rates. This effect on the resulting incidence rate would be in the opposite direction of the effect of limited sensitivity. However, neither extent nor directionality of the resulting bias can be estimated from on the available data.

c. **Risk factors for anaphylaxis and hypersensitivity may be imbalanced between clinical trials and (b) (4) data.** The investigators adjusted only

for age and sex in the SIR comparison with users of other GLP-1 analog drugs and with type-2 diabetic patients. Additional risk factors, such as comedications that may cause hypersensitivity reactions, race/ethnicity, genetic predisposition, previous reactions and other allergies, or concomitant disease (HIV, others), may be imbalanced between clinical trial subjects and the external reference populations, resulting in confounding. However, the investigators did not provide a summary of patient characteristics in (b) (4) data that would allow for an assessment of risk factor balance.

- d. (b) (4) **data include only U.S. patients, while clinical trials were typically multinational.** Similar considerations apply as in Section 3.b, above: the prevalence of risk factors for anaphylaxis and hypersensitivity may differ between countries and bias the comparisons made by the sponsor.

The likely presence of biases with different directionality and extent does not suggest that they necessarily cancel each other out. In fact, SIRs were well below 1.0 for anaphylaxis events among control patients in clinical trials and for hypersensitivity among both lixisenatide exposed patients and controls, compared with (b) (4) data. These observations suggest the possibility that the resulting bias is in favor of the clinical trials and comparisons of lixisenatide patients with external comparators are biased in favor of lixisenatide.

5 CONCLUSION

The sponsor's analyses found that rates of anaphylaxis among lixisenatide-exposed clinical trial subjects were as high, or higher, than expected in an age- and sex- matched external population. Rates for anaphylaxis among clinical trial controls and rates for hypersensitivity reaction among lixisenatide subjects and controls in clinical trials were lower than expected in an external population.

However, due to the limitations outlined in this review, results of incidence rate comparisons between clinical trials and administrative claims data should be interpreted with great caution. These analyses are not able to inform causality and they were not conducted for that reason. At most, these analyses can help understand differences between the clinical trial populations and diabetic patients, including GLP-1 analog users, in clinical practice with regard to anaphylaxis and hypersensitivity. However, even these comparisons are limited by the presence of potential biases. The most valid inferences are those made within the clinical trials, based on randomized treatment.

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APPENDIX

Table 1. List of MeDRA (17.1) Terms and Code for the Anaphylactic reaction by narrow SMQ search

PT_NAME (Anaphylactic Reaction Narrow)	PT_CODE
Anaphylactic reaction	10002198
Anaphylactic shock	10002199
Anaphylactic transfusion reaction	10067113
Anaphylactoid reaction	10002216
Anaphylactoid shock	10063119
Circulatory collapse	10009192
First use syndrome	10068158
Kounis syndrome	10069167
Shock	10040560
Type I hypersensitivity	10045240

Table 2. List of MeDRA (17.1) Terms and Code for the Angioedema by narrow SMQ search

PT_NAME (Angioedema Narrow)	SMQ_PT_CODE
Allergic oedema	10060934
Angioedema	10002424
Circumoral oedema	10052250
Conjunctival oedema	10010726
Corneal oedema	10011033
Epiglottic oedema	10015029
Eye oedema	10052139
Eye swelling	10015967
Eyelid oedema	10015993
Face oedema	10016029
Gingival oedema	10049305
Gingival swelling	10018291
Gleich's syndrome	10066837

Table 2 cont'd.

PT_NAME (Angioedema Narrow)	SMQ_PT_CODE
Hereditary angioedema	10019860
Idiopathic angioedema	10073257
Idiopathic urticaria	10021247
Laryngeal oedema	10023845
Laryngotracheal oedema	10023893
Limbal swelling	10070492
Lip oedema	10024558
Lip swelling	10024570
Mouth swelling	10075203
Oculorespiratory syndrome	10067317
Oedema mouth	10030110
Oropharyngeal swelling	10031118
Palatal oedema	10056998
Palatal swelling	10074403
Periorbital oedema	10034545
Pharyngeal oedema	10034829
Scleral oedema	10057431
Small bowel angioedema	10051401
Swelling face	10042682
Swollen tongue	10042727
Tongue oedema	10043967
Tracheal oedema	10044296
Urticaria	10046735
Urticaria cholinergic	10046740
Urticaria chronic	10052568
Urticaria papular	10046750

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Pharmacovigilance Memorandum

Date: April 4, 2016

Reviewer: Debra Ryan, PharmD, MBA, Safety Evaluator
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Product Name: Lixisenatide

Subject: Sanofi White Paper entitled "Evaluating Hypersensitivity in the Lixisenatide Development Program"

Application Type/Number: NDA 208-471

Applicant/Sponsor: Sanofi

OSE RCM #: 2016-536

1 INTRODUCTION

The purpose of this Pharmacovigilance Memorandum is for the Division of Pharmacovigilance-I (DPV-I) to inform the Division of Metabolism and Endocrinology Products (DMEP) of their evaluation of Postmarketing Section 4 of the sponsor's White Paper entitled "Evaluation of Hypersensitivity in the Lixisenatide Development Program" (see Appendix C). The opinions and conclusion provided by DPV-I from this evaluation will assist DMEP in their review of the safety issue, serious hypersensitivity reactions, for lixisenatide, New Drug Application (NDA) 208-471.

Lixisenatide is a glucagon-like peptide 1 (GLP-1) receptor agonist that is marketed in over 60 countries outside of the US. Lixisenatide is under review by DMEP for the proposed indication as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus. There are five other GLP-1 receptor agonists currently marketed in the US: Byetta (exenatide) approved on April 28, 2005; Victoza (liraglutide) approved on January 25, 2010; Bydureon (exenatide extended release) approved on January 27, 2012; Tanzeum (albiglutide) approved on April 15, 2014; and Trulicity (dulaglutide) approved on September 18, 2014.

During the clinical development program, an imbalance for anaphylactic reactions was seen for the lixisenatide treatment group compared to the placebo group.¹ An allergic reaction adjudication committee (ARAC) identified six patients reported to have experienced an anaphylactic reaction and 10 patients with anaphylactic shock in the lixisenatide treatment group. For the placebo group, the ARAC identified four patients reported to have experienced an anaphylactic reaction and one patient with anaphylactic shock. For the 16 cases of anaphylactic reaction and anaphylactic shock in the lixisenatide treatment group, the ARAC adjudicated that only one case of anaphylactic shock and nine cases of anaphylactic reactions were related to lixisenatide.^{2,3} DMEP has identified anaphylaxis and hypersensitivity reactions as a clinically significant issue and a discussion of the benefits and risks of lixisenatide are scheduled to be discussed at an Advisory Committee meeting on May 24, 2016.⁴

On November 6, 2015, Sanofi submitted a 120-Day Safety Report⁵ that included 47 postmarketing cases of hypersensitivity reactions from the Sanofi global pharmacovigilance database. These hypersensitivity reactions were identified using the Standardized MedDRA Queries (SMQ) Anaphylactic reaction and Angioedema, both with a narrow scope, a search strategy that precluded the identification of other serious hypersensitivity reactions. A list of the Preferred Terms (PT) included in Sanofi's search strategy can be found in Appendix A. The Mid-Cycle Communication between DMEP and the sponsor on January 14, 2016⁶ noted anaphylaxis and hypersensitivity reactions with lixisenatide to be a significant clinical issue and DMEP requested that Sanofi provide the narrative summaries for the 47 postmarketing cases of hypersensitivity reactions reported with lixisenatide use. Sanofi responded by providing a descriptive summary of the cases, a summary line listing of the cases, and copies of the CIOMS reports on February 4, 2016.⁷ The White Paper was submitted on February 26, 2016 as an amendment to the initial response to the Agency's Information Request. The purpose of the White paper was to further evaluate the potential risk of hypersensitivity reactions in patients receiving lixisenatide and included: 1) an SMQ analysis of clinical trial data with MedDRA PTs coded from investigator verbatim terms for hypersensitivity events, and 2) an analysis of the 47 postmarketing cases of hypersensitivity reactions noted in the 120-Day Safety Report.

In the White Paper, Sanofi concluded that the signal for hypersensitivity reactions with lixisenatide is comparable to other products in the GLP-1 receptor agonist drug-class. However, the signal for serious hypersensitivity reactions for the other products in the class was identified after their approval, which led to labeling revisions to include serious hypersensitivity reactions such as anaphylaxis and angioedema in the Warnings and Precautions section of the labels.⁸⁻¹¹ See Appendix B for summaries of findings from the clinical trials regarding hypersensitivity reactions for the US-marketed GLP-1 receptor agonists.

Another GLP-1 receptor agonist, taspoglutide (b) (4) had an observed anaphylaxis rate of 4.3% in Phase 2 trials, resulting in the discontinuation of Phase 3 trials because of the high frequency of serious hypersensitivity reactions.¹² Therefore, differences within the GLP-1 receptor agonist drug-class with respect to the severity and frequency of the hypersensitivity reactions are possible.

2 SUMMARY OF SPONSOR METHODS

2.1 SANOFI SUMMARY ANALYSIS OF POSTMARKETING REPORTS OF HYPERSENSITIVITY REACTIONS WITH LIXISENATIDE

To conduct the analysis of postmarketing reports of hypersensitivity reactions with lixisenatide, Sanofi obtained sales data from IMS and searched their global pharmacovigilance database for case reports. According to *bulk sales* data from IMS, the estimated worldwide lixisenatide postmarketing exposure to lixisenatide was (b) (4) patient-years (PY) through September 30, 2015. The 47 postmarketing reports were retrieved from the Sanofi global pharmacovigilance database for the period from January 7, 2013 (lixisenatide International Birth Date) through July 7, 2015 using the SMQs Anaphylactic reaction and Angioedema, both with a narrow scope. Also note that throughout the White Paper Sanofi uses the term hypersensitivity reactions as though the search strategy they employed is inclusive of a broad spectrum of hypersensitivity events, a determination that DPV-I does not agree with, as the search strategy is specific for PTs associated with anaphylaxis and angioedema.

There were 29 reports coded as non-serious and 18 coded as serious. A high-level summary was provided for the 29 non-serious cases, of which 17 described cases of urticaria and 12 reports of angioedema. A Sanofi pharmacovigilance physician reviewed the 18 serious reports and categorized each into four ‘standardized allergy event categories’ based on the reported adverse event terms and available clinical detail: 1) anaphylactic reaction, 2) angioedema, 3) urticaria, and 4) other hypersensitivity. In addition, Sanofi summarized the 18 cases by the following characteristics: age, sex, reporter, outcome, reporting country, de-challenge and re-challenge, previous allergy to a GLP-1 product, action taken with lixisenatide, and treatment for the reported hypersensitivity event.

Sanofi made the following observations based on their analysis of postmarketing data for hypersensitivity reactions with lixisenatide:

1. The reporting rate for overall hypersensitivity events is 7.6 events per 10,000 patient-year exposure, which they consider quite low.
2. The majority of the events represent non-serious AE reports.
3. Urticaria and angioedema account for most of the reported allergic reactions.
4. Severe hypersensitivity has a reporting rate of 0.65 per 10,000 patient-years.

2.2 DISPROPORTIONALITY ANALYSIS OF POSTMARKETING EVENTS

To assess the relative reporting frequency of hypersensitivity events with lixisenatide and other GLP-1 receptor agonists, Sanofi conducted a disproportionality analysis of hypersensitivity events reported for lixisenatide, albiglutide, dulaglutide, exenatide, and liraglutide against the background of all reports for all products, first using the Sanofi pharmacovigilance database (AWARE) and secondly from the WHO VigiBase database.

Sanofi made the following observations based on their disproportionality analysis of postmarketing data for hypersensitivity reactions with lixisenatide, albiglutide, dulaglutide, exenatide, and liraglutide:

1. The analysis of the AWARE database revealed no safety signal for hypersensitivity with lixisenatide.
2. The reporting frequency of lixisenatide-associated allergic events in the AWARE database is comparable to the reporting frequency of like events across the background of all drugs in the AWARE database.
3. The results comparing lixisenatide to all drugs in the WHO VigiBase database failed to meet the standard signal definition for all hypersensitivity reactions, although a trend toward higher reporting was noted with the angioedema SMQ.
4. There was no signal for hypersensitivity for any of the GLP-1 receptor agonists in the VigiBase analysis.

Sanofi stated the following regarding their disproportionality analysis:

Direct comparisons between the disproportionality scores for different compounds must be made with caution, as differences in drug surveillance, data collection, event coding by Sponsor companies, time on the market, marketing countries, and local pharmacovigilance system management may all impact the numbers of cases collected and categorized for a given product. Thus, direct comparisons of the risk for hypersensitivity between different members of the GLP-1 RA class cannot be made. While disproportionality analyses can be used to detect potential signals and generate related hypotheses, they cannot be used in isolation to establish causality or lack thereof.

3 DISCUSSION

3.1 DPV-I COMMENTS ON SANOFI SUMMARY ANALYSIS OF POSTMARKETING REPORTS OF HYPERSENSITIVITY REACTIONS WITH LIXISENATIDE

DPV-I finds three areas of concern regarding the methods used by Sanofi in their summary analysis of postmarketing reports of hypersensitivity reactions with lixisenatide: 1) the search strategy employed is not sufficiently broad to capture the range of all possible hypersensitivity reactions, 2) there is inconsistent and incomplete information in the summary, and 3) there are potentially significant but unknown effect from underreporting. Each concern is further discussed below.

Search Strategy

It is the practice in DPV-I to select a search strategy that will provide the highest number of potential cases for the AE being assessed. Sanofi, however, limited the search of their database to the MedDRA PT's in the Anaphylactic reactions SMQ and Angioedema SMQ and uses the term hypersensitivity reactions interchangeably with anaphylaxis and angioedema as if the search strategy was inclusive for all potential hypersensitivity events. Limiting the scope to a narrow search is not a concern for these particular SMQs because the additional PTs in the broad scope would yield too many false positive reports that are generally related to cardiac events. However, Sanofi's search strategy could have included the Hypersensitivity (SMQ) to retrieve reports of other types of severe hypersensitivity reactions such as Stevens-Johnson syndrome.

Inconsistent and Incomplete Information

Sanofi provided inconsistent information in presenting their case series analysis. On page 22 of the White Paper, Sanofi states that the 18 serious AE reports are shown in Section 7.6; however, the table in Section 7.6 lists *only* 16 reports. In reconciling the information from Sanofi's initial response on February 4, 2016, DPV-I noted that the summary states, "The 18 serious cases included: Anaphylactic reaction (1 case), Anaphylactic shock (1 case), Shock (with blood pressure decrease, 1 case), Angioedema (3 cases), Lip swelling, Swelling face, Swollen tongue, and Urticaria (11 cases)," which *only* accounts for 17 cases, not 18 as stated. Additionally, in the two statements summarizing the corrective treatment and recovery from event, the number of cases for which no information was reported is listed as "the rest" and "the remaining cases." DPV-I was able to confirm that 18 serious cases were presented in the line listing submitted in Sanofi's initial response; the two missing cases were coded with the PTs 1) swollen tongue in one case, and 2) hypersensitivity and urticaria in the other case.

It is outside the scope of this review to re-assess the data submitted by Sanofi. Therefore, DPV-I did not perform a comprehensive analysis for inconsistent and incomplete data in Sanofi's report. However, the serious cases are the most relevant type of cases in determining the severity of an adverse event, and it appears that little attention to detail was put into the analysis of these most relevant cases, resulting in the inconsistent reporting of the number of serious cases reviewed.

Relevance of Calculated Reporting Rates

Underreporting is a recognized limitation of spontaneous reporting and one for which the magnitude cannot be determined. According to Sanofi, lixisenatide is currently approved in over 60 countries; however, the 47 postmarketing cases of hypersensitivity reactions represent only ten countries. Additionally, the reporting rates calculated by Sanofi are not true rates. The numerator and denominator are from two different populations with significant inherent variability in how the numerator and denominators were ascertained. Sanofi's calculated reporting rates do not inform on the risk of hypersensitivity associated with lixisenatide.

3.2 DISPROPORTIONALITY ANALYSIS OF POSTMARKETING EVENTS

In pharmacovigilance, the term data mining (DM) refers to the application of statistical algorithms to large drug safety databases in order to detect patterns or associations between drugs and adverse events. Most DM methods detect a disproportionate reporting of a particular event for a drug product in a database relative to a background—usually the entire database.¹³

For the disproportionality analysis in the AWARE database, Sanofi used the proportional reporting ratio (PRR) with corresponding chi-square value “to compare the observed count for a product-event combination with an ‘expected’ count.” A signal is considered to be positive if the threshold of $PRR > 2$, $PRR \text{ chi-square} > 4$, and the number of reports ≥ 3 are met. Sanofi presented limited information on the methods used in their disproportionality analysis; however, these thresholds are consistent with the European Medicines Agency's (EMA) signal detection threshold as defined in the “Guideline on the Use of Statistical Signal Detection Methods in the EudraVigilance Data Analysis System”.¹⁴ The EMA document further states that the thresholds are empirical and that there are no universal thresholds for signals of disproportionate reporting. Additional information that Sanofi should have provided regarding the methods used in their disproportionality analysis should have included a description of the database used, a description of the data mining tool used or an appropriate reference, and a careful assessment of the individual case reports as listed in the Agency's guidance *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*.¹⁵

At present, there are no FDA standards or pre-defined thresholds using DM scores for determining causality or expectedness. Data mining methods cannot be used to conclude or refute whether there is a causal relationship between a drug and an adverse event. DPV-I uses the results of DM for screening FAERS to identify potential signals. These signals are always evaluated in the context of other data sources. Furthermore, DPV-I considers certain events, such as anaphylaxis, serious adverse drug reactions and thus, warrants review of the individual adverse event reports, regardless of the DM score.

Sanofi acknowledges a few of these limitations by noting that differences in drug surveillance, data collection, event coding, time on the market, marketing countries, and local pharmacovigilance system management may impact the numbers of cases collected and categorized for a given product. Sanofi further stated, “direct comparisons of the risk for hypersensitivity between different members of the GLP-1 RA class cannot be made.”

4 REVIEWER'S COMMENTS

Anaphylaxis and serious hypersensitivity reactions remain a safety issue for lixisenatide, and the evidence presented by Sanofi regarding their postmarketing experience with lixisenatide does not advance our knowledge about this risk. In addition, focusing only on anaphylaxis and angioedema does not provide a comprehensive view of the immunogenic potential of lixisenatide. An analysis of all serious hypersensitivity reactions reported for lixisenatide would inform about the occurrence of other severe hypersensitivity reactions (e.g., Stevens Johnson Syndrome, Toxic Epidermal Necrolysis, and Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome).

Spontaneous reporting is a useful source of information for postmarketing surveillance, but there are inherent limitations when assessing individual spontaneous reports. Sanofi's analysis of the 47 postmarketing cases of hypersensitivity reactions from their pharmacovigilance database does not inform about the safety signal identified in the clinical development program. Because spontaneous reporting databases are biased in ways that cannot be measured or controlled, no conclusion can be drawn from spontaneous reporting with respect to the frequency of a reaction for either one drug or a drug-class.

DM in pharmacovigilance is evolving and there are currently no universally accepted guidelines or standards for the methods chosen by an individual company or a regulatory agency. The limitations of data mining include the same limitations inherent to all spontaneous reporting databases and DPV-I does not employ the use of DM scores to refute a potential safety issue identified in a drug products clinical development program.

5 ADDENDUM (MARCH 29, 2016)

On March 17, 2016, an information request was sent for Sanofi to conduct a more comprehensive analysis of their pharmacovigilance database using the MedDRA SMQ Hypersensitivity (narrow scope). Sanofi provided a response on March 28, 2016 to address the above request (See Appendix D).

Sanofi's search of their pharmacovigilance database using the SMQ Hypersensitivity (narrow) for lixisenatide identified 178 reports; 28 serious and 150 non-serious reports, a substantially greater number than previously reported. In the aggregate analysis of these cases, Sanofi reports that three patients received epinephrine as corrective treatment; however, in reviewing Sanofi's response, DPV-I identified four cases (Case ID 2015SA033621, 2013SA128892, 2014SA117202, and 2015SA025220). Cases requiring corrective treatment with epinephrine are indicative of an anaphylactic reaction. As stated previously, it is outside the scope of this review to re-assess the data submitted by Sanofi; however, reports of anaphylaxis are the most significant under review and it appears that little attention to detail was put into their analysis leading to inconsistent data in Sanofi's report.

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7 APPENDICES

7.1 APPENDIX A. PREFERRED TERMS INCLUDED IN THE SMQs FOR ANAPHYLACTIC REACTION AND ANGIOEDEMA – NARROW SCOPE

Angioedema (SMQ) Narrow scope	Anaphylactic reaction (SMQ) Narrow scope
Allergic oedema	Anaphylactic reaction
Angioedema	Anaphylactic shock
Circumoral oedema	Anaphylactic transfusion reaction
Conjunctival oedema	Anaphylactoid reaction
Corneal oedema	Anaphylactoid shock
Epiglottic oedema	Circulatory collapse
Eye oedema	Dialysis membrane reaction
Eye swelling	Kounis syndrome
Eyelid oedema	Shock
Face oedema	Shock symptom
Gingival oedema	Type I hypersensitivity
Gingival swelling	
Gleich's syndrome	
Hereditary angioedema	
Idiopathic angioedema	
Idiopathic urticaria	
Intestinal angioedema	
Laryngeal oedema	
Laryngotracheal oedema	
Limbal swelling	
Lip oedema	
Lip swelling	
Mouth swelling	
Oculo-respiratory syndrome	
Oedema mouth	
Oropharyngeal swelling	
Palatal oedema	
Palatal swelling	
Periorbital oedema	
Pharyngeal oedema	
Scleral oedema	
Swelling face	
Swollen tongue	
Tongue oedema	
Tracheal oedema	
Urticaria	
Urticaria cholinergic	
Urticaria chronic	
Urticaria papular	

7.2 APPENDIX B. SUMMARY OF HYPERSENSITIVITY REACTIONS FROM CLINICAL DEVELOPMENT PROGRAMS OF APPROVED GLP-1 AGONISTS

GLP-1 Agonist (approval date)	Hypersensitivity Reactions Identified
Exenatide (April 28, 2005)*	<ul style="list-style-type: none"> No cases of anaphylaxis reported during clinical development program
Liraglutide (January 25, 2010)*	<ul style="list-style-type: none"> Two patients with potentially anaphylactic events Two patients that discontinued drug due to hypersensitivity
Albiglutide (April 15, 2014)†	<ul style="list-style-type: none"> Systemic Allergic Reactions 1.8% in albiglutide treatment group vs. 1.9% in placebo group Angioedema 3 (0.1%) in albiglutide treatment group vs. 5 (0.2%) in all comparators Anaphylaxis Reaction 1 (0.0%) in albiglutide treatment group vs. zero in all comparators
Dulaglutide (September 18, 2014)*	<ul style="list-style-type: none"> Overall hypersensitivity reactions 7 (0.3%) in dulaglutide treatment group vs. 5 (0.7%) in placebo One case of anaphylactic shock and one case of Stevens-Johnson syndrome in dulaglutide treatment group

* Balakrishnan S, Clinical Review of BLA 125469 Trulicity (dulaglutide). 13Aug14. DARRTS Reference ID 3609106.

† Vasisht K. Clinical Review of BLA 125431 Tanzeum (albiglutide). 04Nov13. DARRTS Reference ID 3400785.

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/s/

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CHRISTIAN T CAO
04/04/2016

CINDY M KORTEPETER
04/04/2016

ROBERT L LEVIN
04/04/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Devices and Radiological Health

Office of Compliance, Division of Manufacturing and Quality

Respiratory, ENT, General Hospital, & Ophthalmic Devices Branch

DATE: September 22, 2015

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Center for Devices and Radiological Health (CDRH)

**Rakhi M.
Panguluri -S**

Digitally signed by Rakhi M. Panguluri -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
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Date: 2015.09.23 17:19:58 -04'00'

From: Christopher J. Brown, Mechanical Engineer, REGO/DMQ,/OC/ CDR,
WO66-3428

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Application #

NDA 208471

Product Name:

Lixisenatide pen-injector

Consult

1. CDER has requested:

Instructions:

- a. CDRH/OC to perform review of the application for deficiencies related to 21 CFR 820,
- b. CDER has requested that site appropriate to be inspected are identified: addressed in this review.

The Office of Compliance at CDRH received consult for NDA 208471, from CDER to review of the application for deficiencies related to 21 CFR 820, and evaluate NDA 208471 and identify the appropriate inspections site(s) for the combination product identified in the application.

Additionally, EIR for Sanofi-Aventis Deutschland GmbH, from 6/24/2013 to 7/02/2013 was consulted for this review.

Background

Sanofi-Aventis manufactures a Class II combination product consisting of a drug cartridge (Lixisenatide) inside of a medical device (injection pen). The product is intended for use by type 2 diabetes patients and is a once-daily prandial GLP-1 receptor antagonist (RA) for use in combination with basal insulin. According to Sanofi-Aventis, it is indicated for patients with type 2 diabetes mellitus when the following do not provide adequate glycemic control: diet and exercise (b) (4)

(b) (4)

The lixisenatide pen-injector is a disposable device combined with a cartridge that is used to dispense fixed doses of lixisenatide. It is a fully mechanical device, containing no electronic components. With regard to appearance and general handling characteristics, the lixisenatide pen-injector is similar to other disposable pen-injectors.

The lixisenatide pen-injector dispenses fourteen fixed doses of 0.2 mL. A dose is set by pulling out the button. The lixisenatide pen-injector is available for two different dosage strengths (Figure 1): 10 μ g and 20 μ g per 0.2 mL administration volume. The body and cap are provided in two different colors: green (10 μ g) and burgundy (20 μ g).



Concentration per dose (0.2 mL)	10 µg	20 µg
Concentration per mL	0.05 mg/mL	0.1 mg/mL
Color of pen	Green	Burgundy
Tactile feature on cap and button	Lines	Circles

Figure 1. Lixisenatide pen-injectors with different colors and tactile features

In addition, each strength bears differently shaped grip features on the button and on either side of the pen cap: lines (green pen) (Figure 2, Figure 3) and circles (burgundy pen). Apart from color and grip features, the geometry and function of each pen variant is identical, according to the firm.

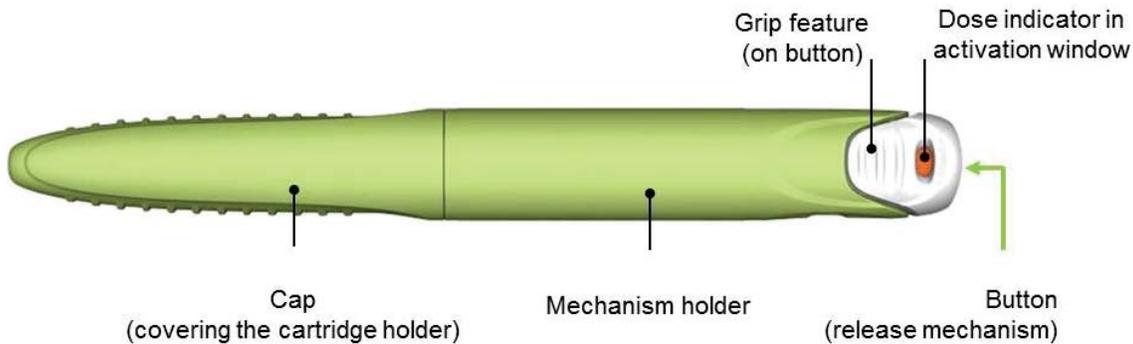


Figure 2. Lixisenatide pen-injector (closed cap – top view)

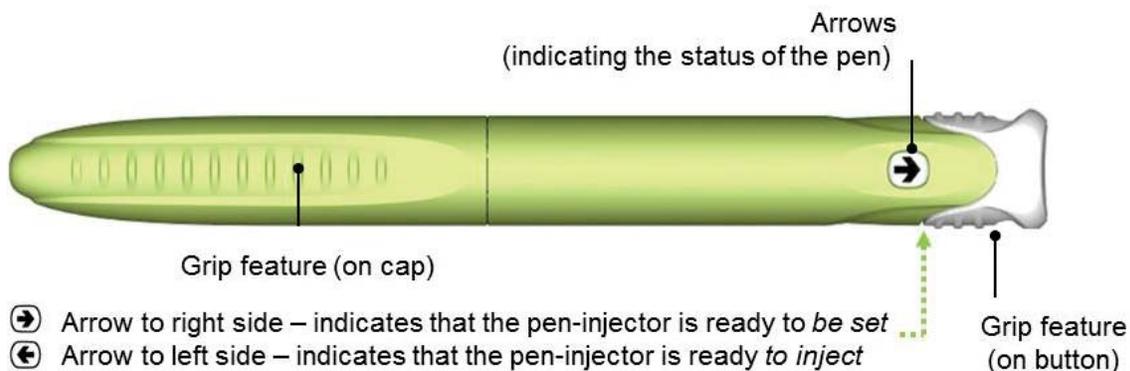


Figure 3. Lixisenatide pen-injector (closed cap – side view 1)

A new pen must be activated. Orange color on dose button window indicates a new pen which requires activation before injecting the first dose. White color on dose button window indicates an activated pen which is ready for injection.

Once a dose is set, the button cannot be returned to its starting position without dispensing any fluid. The dose is dispensed by pressing the button fully back into the body and subsequently maintaining pressure (with the needle in place within the patient) on the button for 2 seconds without retrieving the needle.

The cartridge contains the drug product to be dispensed by the device and which is (b) (4) assembled with the pen-injector. The cartridge consists of a (b) (4) tube, sealed at both ends with rubber components. The rubber component at the needle-end is the rubber seal. When the pen-injector is in use, the rubber seal is pierced by the needle to allow fluid to flow from the cartridge. The rubber component at the opposite end, the button-end, of the cartridge, is the plunger which is moved by the pen mechanism, forcing fluid through the needle. The cartridge provides a hermetic seal

around the medication, maintaining its sterility prior to use. Figure 4 shows the pen with the cap removed.

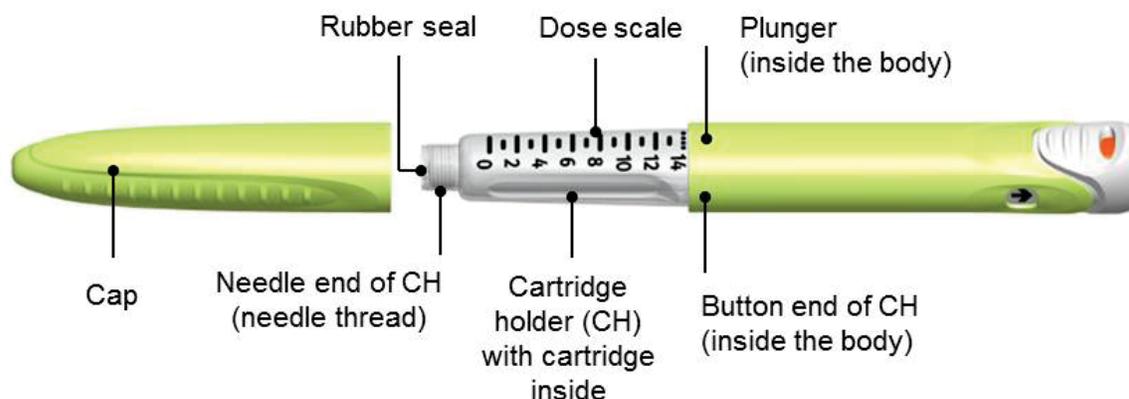


Figure 4. Lixisenatide pen-injector (cap taken off)

According to the firm, the lixisenatide pen-injector has no direct contact with the drug product. The cartridge (primary packaging) is filled (b) (4) and sealed with a rubber seal. The cartridge is inserted into the cartridge holder of the pen-injector, which, by itself, is not sterile. When a sterile pen needle is attached to the needle thread of the cartridge holder, only the sterile end of the needle punctures the rubber seal of the cartridge. The sterile drug solution is solitarily in contact with the sterile pen needle when the pen needle is attached to the pen-injector. When pen needle and rubber seal of the cartridge are connected, the "fluid pathway" is created. A dose is administered through the fluid pathway when the drug solution flows from the cartridge through the needle into the patient's body. No part of the pen-injector is in direct contact with the drug product solution or fluid pathway.

A needle must be attached to the thread on the cartridge-end of the device by screwing it onto the cartridge holder. An orange color appears in a window in the button before activation of the pen-injector (Figure 5 "New pen (not activated)"). When the activation step is performed, the color displayed within the window changes from orange to white (Figure 5 "Pen ready for injection (activated pen)"). The activation step comprises of loading the pen by pulling the injection button axially away from the needle in the direction of the arrow until the end stop is reached (Figure 6) and a "click" can be heard or felt.



New pen (not activated)



Pen ready for injection (activated pen)

Figure 5. - Activation window



Figure 6. Loading the pen-injector (dose setting)

When the button is fully extended, the arrow changes direction in the window located on the pen body and points towards the needle, indicating that the pen is ready for dispensing the dose. Once a dose is set, the button cannot be returned to its starting position without dispensing any fluid. The dose is dispensed by pressing the button fully back into the body until a tactile stop prevents any further movement and subsequently maintaining pressure (with the needle in place within the patient) on the button for 2 seconds without retrieve the needle. (b) (4)

. The subsequent dose can only be set when a dose has been completed.

Design Controls Review

The firm provided a copy of the FRA-SOP-02036 Design Control. This SOP describes the development process of a medical device and its components (including changes to marketed devices, when requested by a sponsor). The document outlines staff responsibilities and training. Further, it describes the design process, each stage in

detail and lists the applicable SOPs for design transfer, design changes, design history file, human factors and engineering validation, verification, risk management, and design input and output.

The firm described the design process stages. The device design process at Sanofi following the (b) (4) (Figure 1) is organized in five different stages:



Figure 7. Sanofi Device Development Model

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The firm's submission is adequate. Their description of the documentation and requirements of their [REDACTED] (b) (4) program appear to repeat the 21 CFR 820.50, requirement. But the firm provides sufficient documentation to substantiate the descriptions.

Regulatory history evaluation

Facility which may be subject to applicable Medical Device Regulations under 21 CFR part 820:

Establishment (Applicant):

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Fax: (877) 332-5512

FEI: 3003596612

Role: Applicant – US Headquarters

Reviews:

I. Facility Inspection:

Inspection [REDACTED] (b) (4)

Classified: NAI

This high priority CDER Sponsor inspection of Sanofi-Aventis U.S. LLC was initiated pursuant to an assignment memorandum dated 2/2/2015 from the Good Clinical Practice Assessment Branch (GCPAB), Division of Clinical Compliance Evaluation (DCCE), Office of Scientific Investigations (OSI), FACTS Assignment #11509997, OP ID # 7807659. Inspectional guidance was provided through CP 7348.810 (SPONSORS, CONTRACT RESEARCH ORGANIZATIONS AND MONITORS). [REDACTED] (b) (4)

[REDACTED]

(b) (4) A Form FDA 483, Inspectional Observations, was issued at the conclusion of the inspection regarding the following: serious and unexpected adverse drug experiences were not always reported to the FDA within 15 calendar days and annual reports did not include the status of each post marketing study.

Since the facility has been inspected twice within the last two years, resources are limited and the manufacturer and applicant are part of the same firm, a pre-approval inspection of the applicant's facility is not required.

II. Facility Inspection:

Facility which may be subject to applicable Medical Device Regulations under 21 CFR part 820:

Establishment (Manufacturer)
Sanofi-Aventis Deutschland GmbH
Brüningstraße 50
Industriepark Höchst
65926 Frankfurt am Main, Germany
Phone: +49 0 69 305165
FEI: 3003195501

Reviews:

III. Facility Inspection:

(b) (4). Classified VAI. Unfortunately, there was no device CSO on this inspection, and the inspection was focused on drug product and API manufacturing. (b) (4)

In general, as part of the Quality System coverage, they covered complaints, FARs and BPDRs, deviations/events/manufacturing investigations, changes, stability, batch record reviews, and various validations. Some of this review did overlap with what would be normally covered in a device inspection.

(b) (4) Classified NAI: This pre-approval and current GMP inspection of an API manufacturer was conducted per FACTS assignment #8945079 and in accordance with CP 7356.002F (API), 7356.002 (Drug Manufacturing Inspections) and 7346.832 (Pre-Approval Inspections). (b) (4)

(b) (4) This inspection covered Quality, Facility & Equipment, Materials, Production, and Laboratory Systems.

Since the facility has not been inspected for medical devices within the last two years, and the manufacturers responsibilities are critical a pre-approval inspection of the applicant's facility is required.

Note to CDER: CDRH, Office of Compliance recommends device inspection of the manufacturing facility of the combination product.

Deficiencies to be conveyed to the applicant

There are no outstanding deficiencies to be conveyed to the applicant.

CDRH Office of Compliance Recommendation

The Office of Compliance (OC) at CDRH has completed the evaluation of application - NDA 208471 and has the following recommendation:

Application Lixisenatide pen-injector approvability under the Medical Device Regulations should be delayed until the inspection of Site one Sanofi-Aventis Deutschland GmbH has been conducted and the site is deemed acceptable.

Christopher J. Brown -S
2015.09.23 15:47:08 -04'00'

Christopher J Brown, P.E., MLT (ASCP)

Prepared: Christopher J Brown: 09/23/2015

Reviewed: RDalal: 09/23/2015

CTS No.: ICC1500028

Application Number: NDA 208471

Inspectional guidance

CDRH recommends the inspection under the applicable Medical Device Regulations of:
Establishment (Manufacturer)
Sanofi-Aventis Deutschland GmbH
Brüningstraße 50
Industriepark Höchst
65926 Frankfurt am Main, Germany
Phone: +49 0 69 305165
FEI: 3003195501

- (1) A comprehensive baseline Level 2 inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30)

Additionally, evaluate the manufacturing activities associated with the manufacturing/assembly of the finished combination product, including in process and final acceptance activities. Detailed inspection guidance will be provided upon request. Questions regarding this consult should be referred to one of the following individuals:

Primary Contact

Christopher J Brown, P.E., MLT(ASCP)
Mechanical Engineer,
Respiratory, Ear/Nose/Throat, General Hospital, and Ophthalmic Devices Branch
(REGO), Division of Manufacturing Quality (DMQ)
Office of Compliance (OC), WO66 RM 2643A
Phone: 301-796-0380

Secondary Contacts (if Primary is unavailable and a timely answer is required)

Rakhi M. Dalal, Ph.D., Toxicologist
REGO/DMQ/OC
WO66 RM 3454
Phone: 301 796 6418

**THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM
DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL
INFORMATION**

There was no attachment contained within this review

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANIKA A LALMANSINGH

04/02/2016

Uploading on behalf of Christopher J. Brown.

LABEL, LABELING, AND HUMAN FACTORS RESULTS REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: March 22, 2016

Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)

Application Type and Number: NDA 208471

Product Name and Strength: Lixisenatide Injection, 150 mcg/3 mL (50 mcg/mL) and 300 mcg/3 mL (100 mcg/mL)

Product Type: Combination Product (Drug + Device)

Rx or OTC: Rx

Applicant/Sponsor Name: Sanofi

Submission Date: July 27, 2015

OSE RCM #: 2015-1702

DMEPA Primary Reviewer: Sarah K. Vee, PharmD

DMEPA Team Leader: Yelena Maslov, PharmD

DMEPA Deputy Director: Lubna Merchant, MS, PharmD

1 REASON FOR REVIEW

On July 27, 2015 Sanofi submitted NDA 208471, lixisenatide injection, for review by the FDA. They submitted container label, carton labeling, instructions for use (IFU) and human factors (HF) validation study results. DMEP requested that we review the materials from the medication error perspective.

2 BACKGROUND

An NDA for lixisenatide was originally submitted on December 20, 2012 but was subsequently withdrawn on September 10, 2013 following discussions with the Agency regarding the proposed process for review of the interim data from the cardiovascular outcomes trial EFC11319 (ELIXA).

Sanofi resubmitted the same human factors validation study results that were submitted previously under NDA 204961 that was reviewed in OSE Review #2013-206. As outlined in Table 1, discussions regarding failures observed in the human factors validation study was discussed with Sanofi.

Table 1: Timeline describes the requests, submissions, and reviews to date:

Date	Synopsis
March 25, 2011	The Applicant originally submitted the proposed Usability Validation Study and Delta 14 pen-injector IFU in IND 062724
May 17, 2011	The Applicant submitted an updated protocol replacing the March 25, 2011 submission. The revised protocol included changes from the sponsor to proceed with a one-step dose initiation regimen and a development of two dose strengths (b) (4).
June 1, 2011	DMEPA provided recommendations regarding the HF Validation Study protocol, IFU, and device to the Applicant via a letter.
February 7, 2012	The Applicant submitted responses to the comments provided on June 1, 2011
March 27, 2012	DMEPA provided further recommendations and comments regarding the HF Validation Study protocol and IFU in OSE #2012-416
December 20, 2012	The Applicant submitted Human Factors/Usability Report, carton and container label, and the IFU for review in NDA
September 10, 2013	Information Request (IR) sent regarding errors in human factors study results regarding the removal of the needle step, five participants experienced needle sticks.
October 15, 2013	Type A Meeting: Discussion occurred regarding the IR (post meeting)
December 12, 2014	Sanofi submit response to IR and Type A Discussion Item. DMEPA memo dated February 2, 2015 (OSE # 2014-2607) finding Sanofi response acceptable.

3 MATERIALS REVIEWED

We considered the materials listed in Table 2 for this review. The Appendices provide the methods and results for each material reviewed.

Table 2. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	D

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA reviewed the proposed labels and labeling and the human factors study results provided by Sanofi on July 27, 2015. We previously reviewed and provided comments regarding the human factors validation studies and results and agreed with the study objectives, methodology, and mitigation strategies (See Table 1). Overall, the results demonstrate that trained patients and healthcare providers (HCP) can safely and effectively use the proposed device to administer lixisenatide.

4.1 HUMAN FACTORS STUDY

We agree with Applicant's study design for Lixisenatide in terms of objective, participants, tasks, and use environments (See Appendix C for the study design and results). We note that in the first HF summative study, failures and difficulties were observed with the activation step and attaching and removal of the needle in the untrained group. The Applicant assessed these failures and made further improvements to the IFU to mitigate the risk involving the activation step and needle attachment. These changes were tested in a supplemental HF study. The results are discussed below.

4.1.1 Differentiation

There were no failures in differentiating between the 10 mcg per dose and 20 mcg per dose Lixisenatide pens for all participants (16 Health Care Professionals and 18 Patients). Therefore, the pens are well-differentiated between each other and among other pens.

4.1.2 Comprehension/Readability

The participants (15 type 2 DM patients) were able to find answers in the IFU in a reasonable time. One participant had some difficulties in answering the question if he could store the pen with a needle attached. He answered that he would ask his doctor about this question.

4.1.3 Usability

The critical tasks failures during the validation study occurred with 1) attachment the needle and removing the caps, 2) discarding priming/activation dose, and 3) injecting first dose. In all of the tasks, failures occurred only with untrained patients and HCP who did not read the IFU or had a physical condition, making the task difficult. All trained patients and HCPs either performed these tasks with success or success with difficulty or effort.

The first set of failures occurred with the task of attaching the needle and removing caps. However, we note that this failure is related to the needle and not the device. In fact, during our post-marketing surveillance we identify multiple medication errors involving incorrect attachment of the needle and not removing the inner needle cap. As a result, this failure does not affect the usability of the pen device itself.

The most common failure that occurred in both the validation and re-validation study was discarding the priming/activation dose, which may result in an injection of an incomplete first dosage. Participants who fail to discard the activation step and inject it as the first dose will receive a dose that is around 65% of the full dose. This means that for a 10 mcg dose, the patient will receive 6.5 mcg as their first dose and for a 20 mcg dose, 13 mcg would be injected as their first dose, which reduces their overall monthly dose by less than 2.5% resulting in minimal to no impact on the patient's HbA1C. Thus, the harm from not injecting the full dose is minimal because the activation step is only performed once for each new pen device. In addition, this failure occurred only in untrained participants and participants who were trained were able to perform the activation step properly. As a result, we find the study results acceptable since the harm resulting from not performing activation step or doing it incorrectly is minimal.

Overall, validation and re-validation studies demonstrate that the pen design and packaging are acceptable to ensure safe and effective use of the product by representative end users. However, despite the Applicant's use of visual cues to help users understand how to use and activate the pen, errors still occurred with activation step and use of needles with untrained participants. We conveyed our concerns previously to the Applicant, as outlined in Section 2, and agreed with the labeling changes proposed by the Applicant to address this issue.

5 CONCLUSION & RECOMMENDATIONS

Overall, the results demonstrate that trained patients and healthcare providers (HCP) can safely and effectively use the proposed device to administer lixisenatide. We also note that the errors that occurred in the untrained group would have minimal clinical impact. Changes to the labeling addresses (i.e. addition of the quick guide on the carton labeling and statement to provide training in the prescribing information and patient package insert) the use failures observed in the human factors studies. Additionally, the IFU and container label can be improved to increase the prominence of important information to promote the safe use of the product.

5.1 RECOMMENDATIONS FOR SANOFI

We recommend the following be implemented prior to approval of this NDA:

1. Instructions for Use (IFU)
 - a. Section 2 - Getting Started
 - i. In step 5, revise the statement (b) (4) to a simpler statement such as “The pen is now ready to use” to better communicate this information to end user. This may prevent end users to activate the pen before each use, as observed during the validation study.
 - b. Section 3 – Daily use of pen
 - i. Relocate the “Injection sites” section to Section 3 under Step C. This should be a separate Step “Choosing Injection Sites”. This information is more appropriate in Section 3 to remind end users, especially first time users, of the appropriate injection sites prior to injecting.
 - ii. In Step D increase the prominence by bolding the statement “You may feel or hear a click”. Participants in the validation study did not understand whether they had already injected themselves.
2. Pen Label
 - a. We recommend adding the route of administration, “For subcutaneous use only.” per 21 CFR 201.100(b)(3) as this device will be used by patients and caregivers at home. If additional space is needed to add that information, consider removing one of the “SANOFI” statements from the label.
3. Provide NDC numbers of pen labels and carton labeling for Agency review.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Lixisenatide that Sanofi submitted on July 27, 2015.

Table 2. Relevant Product Information for Lixisenatide	
Initial Approval Date	N/A
Active Ingredient	Lixisenatide
Indication	a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Route of Administration	Subcutaneous injection
Dosage Form	Injection
Strength	150 mcg/3 mL (50 mcg/mL) and 300 mcg/3 mL (100 mcg/mL)
Dose and Frequency	Initiate at 10 mcg once daily for 14 days. On Day 15, increase dosage to 20 mcg once daily
How Supplied	<ul style="list-style-type: none">● Starter Pack: For treatment initiation, Starter Pack of 1 pre-filled green pen of 10 mcg and 1 pre-filled burgundy pen of 20 mcg● Maintenance Pack: 2 prefilled burgundy pens of 20 mcg● A pack size of 1 prefilled green pen of 10 mcg.● A pack size of 2 prefilled green pens of 10 mcg.
Storage	Prior to first use, Lixisenatide should be stored in a refrigerator, 36°–46°F (2°C–8°C). Do not freeze. Keep the prefilled pen in the original package to protect it from light. After first use, store below 86°F (30°C). Replace the pen cap after each use to protect from light. Discard pen 14 days after first use.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On March 15, 2016, we searched the L:drive and AIMS using the term, lixisenatide to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified three previous reviews and we confirmed that our previous recommendations were implemented.

Information to include in the citation for previous reviews:

Vee, S. Label and Labeling Review for Lixisenatide IND 62724. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 Feb 2. RCM No.: 2014-2607.

Agustin, R. Human Factors Study Protocol Review for Lixisenatide IND 62724. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 Mar 27. RCM No.: 2012-416.

Agustin, R. Label and Labeling Review for Lixisenatide NDA 204961. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 Jul. RCM No.: 2013-206.

APPENDIX C. HUMAN FACTORS STUDY

C.1 Study Design

Usability Study

8.3.1 Study objective

The objective of the human factors (HF) validation study was to validate that the lixisenatide pen-injector, including the associated instructions, packaging and labeling, could be correctly, safely and effectively used by diabetes patients and HCPs. The study aimed to validate the effectiveness and safety of the lixisenatide pen-injector and procedure for use by the intended user groups, and determine if any aspects of the pen packaging, labeling or instructions ([Appendix 2](#), [Appendix 3](#), [Appendix 4](#) respectively) led to confusion, task failures, use errors with serious potential consequences, or patient safety risks.

The data from the study was used either to validate the pen design, packaging, and instructions for use (IFU) as successful in mitigating risks, or to identify tangible ways to mitigate any significant residual risks identified from the results of the study.

8.3.2 Critical and essential task categorization

In this section, the tasks tested in the HF validation study are identified as critical tasks or essential tasks. Critical tasks are those with a direct effect on user or patient safety. Essential tasks are those associated with use of the device for its intended purpose. [Table 5](#) presents a list of the all tasks that were classified as critical or essential.

In addition to direct measurement of task performance, the following information was collected:

- Behaviors: behaviors were observed, documented and categorized regarding hesitation, confusion or frustration and error (4).
- Subjective: participant feedback was collected, in open-ended narrative form, pertaining to key interactions with the pen, labeling and instructions. Further, participants were probed for their concerns and difficulties related to various tasks and aspects of the procedure and the pen design.

Table 5 – Task categorization including study technique and the range of acceptable performance

Task	Severity level	Task categorization	Study technique	Range of acceptable performance	Subjective responses
Knowledge of pen storage	High	Critical task	Participants will be asked to state where the drug is to be stored.	Must answer "refrigerator" before activation and "room temperature/below 86°" after activation.	Participant verbal response
Understanding of dose frequency	Medium	Critical task	Participants will be asked to state how often they administer the drug.	Must answer "once a day".	Participant verbal response
Understanding of starter treatment	Medium	Critical task	Observation of use	Participants are provided with the standard starter pack and must use the green pen.	Participant verbal response
Safe removal of pen from packaging	Medium	Essential task	Participants will be asked when they should use the purple pen	Must answer "after 14 days, after green pen is finished" or similar.	Subjective commentary on packaging
			Participants will be required to remove the pen from the packaging.	Must open the packaging without injury to self or damage to the pen.	Not applicable
Pen/drug inspection	Medium	Critical task	Participants will be provided a pen with degraded drug and one with normal drug. They will be asked to identify the spoiled drug and the expiration date of the pen with the normal drug. Participants will be asked about any difficulties related to drug visibility/inspection and expiration identification.	Must be able to detect degraded drug and identify expiration date.	Participant verbal response
Identification of acceptable injection site	Low	Critical task	Participants will be asked to state the allowable injection site before any pad is applied to their body.	Must respond "in the upper arm, in the thigh or abdomen".	Participant verbal response
Removal of pen cap	Medium	Essential task	Participants will be observed and interviewed regarding their effort to remove the cap.	Must remove the cap without injury to self or damage to products.	Subjective commentary on cap removal
Check remaining dose	Medium	Essential task	Participants will be provided a pen which is empty. They will be asked to identify that the pen is empty.	Must be able to detect an empty pen. Understand black number markings on cartridge holder.	Not applicable

Task	Severity level	Task categorization	Study technique	Range of acceptable performance	Subjective responses
Attaching the needle and removing caps	Medium	Critical task	Participants will be observed and interviewed regarding their ability to attach a needle to the tip of the pen and removal of both inner and outer needle cap prior to administration.	Must securely attach needle and remove both inner and outer needle caps.	Subjective commentary on needle attachment
Discard priming/activation dose	Medium	Critical task	Participants will be observed and interviewed regarding their ability to dispense the new pen 'activation' (priming) step.	Must dispense the activation dose.	Subjective commentary on activation process
			Participants will be observed to see if they inject a further dose.	Must not inject activation dose followed by regular dose.	
Pinching the skin	Low	Essential task	Participants will be observed regarding their skin pinching technique.	Pinching skin or failure to do so does not constitute a failure.	Not applicable
Inject first/regular dose	High	Critical task	Participants will be observed and interviewed regarding their ability of firmly pushing the button until it cannot go further.	Must depress injection button to administer dose.	Subjective commentary on drug expression
			Participants will be observed regarding their inclination to inject a further dose.	Must hold the injection button for 2 seconds. Understand feedback of injection (click sound and/or movement of the plunger). Should inject only once.	
Proper removal and disposal of needle	Medium	Critical task	Participants will be observed regarding their ability to remove and dispose the used needle.	Must remove needle safely and know how to dispose.	Subjective commentary on needle insertion procedure

8.3.3 Use scenarios tested

Lixisenatide is used chronically for months or years in the treatment of T2DM. Patients initiate treatment by injecting 10 µg dose (using the green pen) daily for two weeks before shifting to the 20 µg dose (using the burgundy pen).

Thus, three pen usage scenarios are possible during the different stages of treatment:

1. Starting the treatment with the green 10 µg pen and afterwards moving to the burgundy maintenance pen.
2. First dose – unpacking and then activating the lixisenatide pen-injector by expelling the activation dose, first dose delivery simulated in the study by injection into a simulated skin pad.
3. Routine dosing – delivery of a dose from an already activated pen-injector, simulated in the study by injection into a simulated skin pad.

For the first scenario, the participants were observed as to whether they used the green pen first. Then the users were asked when they should use the burgundy pen.

The second scenario was investigated (Table 5) through questioning and by observing performance during the following tasks:

- Knowledge of pen storage (inquiry by moderator)
- Understanding of dose frequency (inquiry by moderator)
- Safe removal of pen from packaging (observed)
- Pen/drug inspection (observed)
- Identifying acceptable injection site (observed)
- Removal of pen cap (observed)
- Checking remaining dose (inquiry by moderator and observed)
- Attaching the needle and removing caps (observed)
- Dispensing the priming/activation dose (observed)
- Inject first dose (observed)
- Proper removal and disposal of needle (observed)

The third scenario was investigated (Table 5) by observing performance during the following tasks:

- Removal of pen cap (observed)
- Attaching the needle and removing caps (observed)
- Inject regular dose (observed)
- Proper removal and disposal of needle (observed)

8.3.4.1 Study participants

A total of sixty (60) participants took part in the study, which included 30 T2DM patients (15 trained, 15 untrained; [Figure 39](#)), and 30 HCPs (15 trained, 15 untrained). Patients ranged in age from 18 to 70, with the majority of the participants over age 45. HCPs could be diabetes educators, endocrinologists, nurse practitioner/physician's assistant and/or primary care and specialty physicians. All participants were naïve to the device tested. The majority of the patient group was familiar with some form of diabetes treatment or insulin management routine, including daily injections (via a vial and syringe or an insulin pen) and/or oral medications.

Table 6 – Injections performed by trained patients

Task	Group	Session	Supervised/ unaided	Dose
1	Trained	Session 1 first day	Supervised	New pen, activating and first injection
2	Trained	Session 2 second day	Unaided	New pen, activating and first injection
3	Trained	Session 2 second day	Unaided	Activated pen, next injection including needle change

Table 7 – Injections performed by untrained patients

Task	Group	Session	Supervised/ unaided	Dose
1	Untrained	Session 1 first day	Unaided	New pen, activating and first injection
2	Untrained	Session 1 first day	Unaided	Activated pen, next injection including needle change

Table 8 – Injections performed by trained HCPs

Task	Group	Session	Supervised/ unaided	Dose
1	Trained	Session 2 second day	Unaided	New pen, activating and first injection
2	Trained	Session 2 second day	Unaided	Activated pen, next injection including needle change

Table 9 – Injections performed by untrained HCPs

Task	Group	Session	Supervised/ unaided	Dose
1	Untrained	Session 1 first day	Unaided	New pen, activating and first injection
2	Untrained	Session 1 first day	Unaided	Activated pen, next injection including needle change

Supplemental Validation Study

8.4 SUPPLEMENTAL VALIDATION STUDY

A supplemental human factors validation study was conducted to validate the changes made to the IFU, in response to the results of the previous HF validation study, with regard to attaching the needle and performing the activation step.

8.4.2 Use scenarios tested

During the first HF validation study, critical use errors and difficulties were observed only in the second scenario (see Section 8.3.3). In this study, only the tasks related to that scenario were tested:

- First dose – unpacking and then activating the lixisenatide pen-injector by expelling the activation dose, first dose delivery simulated in the study by injection into a simulated skin pad.

The scenario was investigated (Table 13) by observing performance during the following tasks:

- Safe removal of pen from packaging (observed)
- Removal of pen cap (observed)
- Attaching the needle and removing caps (observed)
- Dispensing the priming/activation dose (observed)
- Inject first dose (observed)
- Proper removal and disposal of needle (observed)

As in the HF validation study, the study plan included measurement of user performance, behavior and subjective feedback.

Table 13 – Task categorization including study technique and the range of acceptable performance

Task	Severity level	Task categorization	Study technique	Range of acceptable performance	Subjective responses
Safe removal of pen from packaging	Medium	Essential task	Participants will be required to remove the pen from the packaging.	Must open the packaging without injury to self or damage to the pen.	Not applicable
Removal of pen cap	Medium	Essential task	Participants will be observed and interviewed regarding their effort to remove the cap.	Must remove the cap without injury to self or damage to products.	Subjective commentary on cap removal
Attaching the needle and removing caps	Medium	Critical task	Participants will be observed and interviewed regarding their ability to attach a needle to the tip of the pen and removal of both inner and outer needle cap prior to administration.	Must securely attach needle and remove both inner and outer needle caps.	Subjective commentary on needle attachment
Discard priming/activation dose	Medium	Critical task	Participants will be observed and interviewed regarding their ability to dispense the new pen 'activation' (priming) step.	Must dispense the activation dose.	Subjective commentary on activation process
Pinching the skin	Low	Essential task	Participants will be observed to see if they inject a further dose.	Must not inject activation dose followed by regular dose.	Not applicable
			Participants will be observed regarding their skin pinching technique.		
Inject first/regular dose	High	Critical task	Participants will be observed and interviewed regarding their ability of firmly pushing the button until it cannot go further.	Must depress injection button to administer dose.	Subjective commentary on drug expression
			Participants will be observed regarding their inclination to inject a further dose.	Must hold the injection button for 2 seconds. Should inject only once.	
Proper removal and disposal of needle	Medium	Critical task	Participants will be observed regarding their ability to remove and dispose the used needle.	Must remove needle safely and know how to dispose.	Subjective commentary on needle insertion procedure

8.4.3 Study participants

As the use errors and difficulties were mainly be observed in the untrained arm, only the untrained arm was included in the study.

A total of fifteen (15) participants who had T2DM were recruited for the study according to the same criteria as were used in the HF validation study (Figure 44).

Table 14 – Injections to be performed by untrained patients

Number of injections	Group	Supervised/unaided	Dose
1	Untrained	Unaided	New pen, activating and first injection

Differentiation

In prior formative/exploratory studies the different colors where tested with color blind participants. The results supported the adequate differentiation with the chosen color concept using a green and purple pen.

8.1.1 Study overview

The purpose of the study was to investigate and validate the differentiability of the lixisenatide pen-injector, compared to other pens on the market as well as compared to other lixisenatide pen-injectors.

The differentiation sessions were conducted in order to establish that the user can differentiate the device against other Sanofi or competitor insulin pens. This is to ensure that the device will not be mistaken with similar devices in the real-world use environment, which could potentially lead to an injection of wrong fluids.

One-on-one usability tests with 34 potential pen users were carried out in Germany at a testing facility in Frankfurt am Main. Each session lasted 15 to 30 minutes. The differentiation of the two different colors (green and purple pen) was also conducted with US participants during the simulated use validation study.

The differentiability of the lixisenatide pen-injector was tested with a HCP and a patient group with 16 (HCP) and 18 (patients) participants who were requested to differentiate between the two dosages pens.

The participants were presented different pen combinations. They were first shown one green or purple pen. After this, a combination of pens was placed on the table in front of the participant and they were asked to pick up the pen presented earlier. A time limit for the tasks was not mentioned to the participants, since this would have made the task less realistic.

Table 4 – Possible combination presented to the participants

Combination	Pen 1	Pen 2	Pen 3	Pen 4
Combination 1	Lantus SoloStar	Lixisenatide pen-injector 10 µg	Apidra SoloStar	. ^a
Combination 2	Lantus SoloStar	Lixisenatide pen-injector 10 µg	Insuman Rapid SoloStar	. ^a
Combination 3	Lantus SoloStar	Lixisenatide pen-injector 10 µg	Lixisenatide pen-injector 20 µg	Novorapid Flexpen
Combination 4	Lantus SoloStar	Lixisenatide pen-injector 10 µg	Lixisenatide pen-injector 20 µg	Lilly Humalog Kwikpen
Combination 5	Lantus SoloStar	Lixisenatide pen-injector 10 µg	Lixisenatide pen-injector 20 µg	Apidra SoloStar
Combination 6	Lantus SoloStar	Lixisenatide pen-injector 10 µg	Lixisenatide pen-injector 20 µg	Insuman Rapid SoloStar
Combination 7	Lantus SoloStar	Lixisenatide pen-injector 20 µg	Novorapid Flexpen	. ^a
Combination 8	Lantus SoloStar	Lixisenatide pen-injector 20 µg	Lilly Humalog Kwikpen	. ^a

^a Only three pens were used in this combination.

After the participants had chosen the pen, they were asked how they differentiated their selected pen from the other pens and how difficult this differentiation was. This was conducted in two different lighting conditions: 100 Lux and 300 Lux, which approximately represents common bedside lighting and normal room lighting. The order of the differentiation tasks was counterbalanced to avoid learning effects.

The combinations were as realistic as possible (eg, pens for short-term insulin, long-term insulin and lixisenatide). For each combination, the worst case scenario (ie, including the most similar pens) was tested.

During the study the participants were allowed to think aloud. After the observation a set of open-end questions were answered by each participant directed toward the task of discrimination between the dosage presentations. These sorts of questions included:

- How did you identify the pen? (possible answers color, shape or labeling)
- How easy was it to identify the pen?
- The HCP group was presented with different pen combinations as well as different packaging combinations to simulate the scenario that a physician or pharmacist gave the prescribed packaging to the patient.

Comprehension/Readability

8.2.1 Study overview

Conduct a user test with the lixisenatide starter pack IFU that examines the readability of the document to understand if a defined target group can find information in the IFU and understand key issues with respect to the safe use of the starter pack pens safe use.

The study was performed with 15 T2DM participants including pen naïve users.

8.2.2 Finding

For each question, the participant was asked to find the answer in the IFU; a response from memory was not considered acceptable. If the participant was initially unable to find the answer, the interviewer used non-leading prompts such as repeating or clarifying the question.

In the following situations, a "difficulty" (D) rating was recorded:

- a participant took more than two minutes to find information in the IFU, or
- a participant was given more than two "permitted prompts", such as repeating the question, before finding the information.

If a participant received a "difficulty" rating, they were still counted as having found the information.

8.2.3 Understanding

Participants were asked to respond, where possible, using their own words. The "indicative answer" in the questionnaire details the information that was required for a correct response. As long as the participant's answer corresponded semantically to the "indicative answer", then it was scored as correct.

Interviewers used their judgment as to whether a participant had demonstrated an understanding. In doing this, they took into account the participant's word choice and emphasis, tone of voice and whether there was any hesitation. If an answer was incomplete or partially incorrect, the interviewer asked non-leading questions to probe the participant's understanding.

The study included the following questions:

- The leaflet says that your starter pack includes two different colored pens. What is the difference between the two pens?
- The leaflet says you must activate your lixisenatide pen before you use it for the first time. Why should you do this?
- What does the leaflet say about if you can use a syringe to withdraw the medication from your lixisenatide pen?
- What does it mean if the activation window on your pen is orange?
- How many doses does each lixisenatide pen contain?
- Imagine you have just removed the needle from your pen and replaced the pen cap. Where should you discard the used needle?
- Which pen must you start your treatment with?
- Where on your body can you inject this medicine?
- Imagine you have attached a needle to your pen and just pulled the injection button out. Which direction will the arrow now be pointing?
- For how many days after activation can you use your pen before you must discard it?
- Imagine that you have just activated your new pen. What does the leaflet say about whether or not you can activate the pen again?
- What does the leaflet say about whether or not you can store your pen with the needle attached?
- Imagine you have inserted the needle into your skin and pressed the injection button all the way in. What should you do next so that you get the full dose?

C.2 Results

The results reported for the usability study include the following:

Table 10 – Results of scenario 1 (start with green pen/10 µg, maintenance with burgundy pen/20 µg), n=15 in each group

Step/task	HCP trained group	HCP untrained group	Patients trained group	Patient untrained group
Understanding of starter treatment	S: 100%	S: 100%	S: 100%	S: 100%

Table 11 – Results of scenario 2 (first dose – unpacking/activating pen-injector; delivery of first dose into skin pad), n=15

Step/task	HCP trained group	HCP untrained group	Patients trained group	Patient untrained group
Knowledge of pen storage	S: 15 (100%)	S: 15 (100%)	S: 15 (100%)	S: 15 (100%)
Understanding of dose frequency	S: 15 (100%)	S: 15 (100%)	S: 15 (100%)	S: 15 (100%)
Safe removal of pen from packaging	S: 15 (100%)	S: 15 (100%)	S: 15 (100%)	S: 15 (100%)
Pen/drug inspection	S: 15 (100%)	S: 15 (100%)	S: 15 (100%)	S: 15 (100%)
Identification of acceptable injection site	S: 15 (100%)	S: 15 (100%)	S: 15 (100%)	S: 15 (100%)
Removal of pen cap	S: 15 (100%)	S: 15 (100%)	S: 15 (100%)	S: 15 (100%)
Check remaining dose	S: 15 (100%)	S: 15 (100%)	S: 15 (100%)	S: 15 (100%)
Attaching the needle and removing caps	S: 15 (100%)	S: 14 (93%) SD: 1 (7%)	S: 13 (87%) SD: 2 (13%)	S: 10 (67%) SD: 4 (26%) F: 1 ^a (7%)
Discard priming/activation dose	S: 15 (100%)	S: 14 (93%) F: 1 (7%)	S: 15 (100%)	S: 10 (67%) F: 5 ^{a, b} (33%)
Inject first dose	S: 15 (100%)	S: 14 (93%) F: 1 ^b (7%)	S: 15 (100%)	S: 15 ^{a, c} (100%)
Proper removal and disposal of needle	S: 15 (100%)	S: 15 (100%)	S: 11 (73%) SD: 4 (27%)	S: 14 (93%) SD: 1 (7%)

a P32 was an injection-naïve patient in the untrained cohort. His interview was atypical and somewhat chaotic. He was confused by the pen needle and did not seem able to follow the instruction or illustration demonstrating inner needle cap removal, so he simulated injection with the inner needle cap still on, and was confused when no liquid was expelled. He seemed frequently unable to remember his own actions or information that he had been given, and became very flustered; for example, he could comment objectively on his confusion over the needle cap soon afterwards, but was later unable to describe it. Partway through the interview he told the moderator "I'm sorry, my mind works slowly, I have ADD" which was a potential credible explanation of the behavior seen. His post-assessment interview was terminated in the interests of his well-being, as he did not seem able to give coherent feedback on the instructions or his actions, and seemed stressed. Nevertheless, this patient did understand and demonstrate the key operating sequence for the use of the pen during his assessment session.

b One untrained patient who failed the activation step the first time performed a second activation step correctly after reviewing the IFU.

c This includes the participants who failed in the previous step.

Table 12 – Results of scenario 3 (routine dosing – delivery of from activated pen-injector into skin pad), n=15

Step/task	HCP trained group	HCP untrained group	Patients trained group	Patient untrained group
Removal of pen cap	S: 15 (100%)	S: 15 (100%)	S: 15 (100%)	S: 15 (100%)
Check remaining dose	S: 15 (100%)	S: 15 (100%)	S: 15 (100%)	S: 15 (100%)
Attaching the needle and removing caps	S: 15 (100%)	S: 15 (100%)	S: 15 (100%)	S: 15 (100%)
Inject regular dose	S: 15 (100%)	S: 15 (100%)	S: 13 (87%) SD: 2 (13%)	S: 15 (100%)
Proper removal and disposal of needle	S: 15 (100%)	S: 15 (100%)	S: 15 (100%)	S: 15 (100%)

- A. There were three categories of *failures*: attaching the needle and removing caps (n=1), discarding priming /activation dose (n=5), and injecting first dose (n=1).
1. Attaching the needle and removing caps (n=1)
 - i. Participant 32 (untrained, injection naïve patient): Failed to discard the inner needle cap throughout the whole process resulting in no medication received. Patient was confused by the pen needle and did not seem to follow the instruction or illustration demonstrating inner needle cap removal. Patient told moderator “I’m sorry my mind works slowly, I have ADD.” Post-assessment interview was terminated in the interest of his well-being.
 2. Discarding priming/activation dose (n=5)
 - i. Participant 33 (untrained patient): Failed to press the injection button all the way in during activation step resulting in an injection of an incomplete first dosage. Patient had tendonitis, but it cannot be determined whether this affected her performance. In subsequent trial, she demonstrated learning how to press the injection button firmly all the way in after she got familiar with feeling.
 - ii. Participant 58 (untrained patient): Failed to press the injection button all the way in during activation step resulting in an injection of an incomplete first dosage. Injection window had turned partially, not wholly white. She was confused by the pen state but proceed with the injection. In subsequent trial, she demonstrated learning how to press the injection button firmly all the way in after she got familiar with feeling.
 - iii. Participant 53 (untrained patient): Failed to attach a needle when performing the activation step resulting in an injection of an incomplete first dose. Patient missed Step 2 in the IFU (needle attachment step)
 - iv. Participant 36 (untrained patient): Failed to push the injection button to discard activation step resulting in an injection of an incomplete first dosage. Patient thought that pulling the injection button out was all that was required for activation, and therefore injected the activation dose. She was

comparing the pen being tested with her own syringe which requires pulling the plunger only.

- v. Participant 52 (untrained HCP): Failed to discard the activation step resulting in an incomplete first dosage. She injected the activation dose on the skin pad and when realized her error, she said that she would seek advice on the quantity of the activation fluid and the advised course of action.

3. Injecting first dose (n=1)

- i. One untrained HCP failed to inject first dose. No further information provided.

B. There were three categories of *success with difficulties or effort in*: attaching the needle and removing caps (n=7), discarding priming /activation dose (n=2), proper removal of needle (n=5).

1. Attaching the needle and removing caps (n=7)

- i. Seven participants (1 untrained HCP, 2 untrained patients, and 4 trained patients; none with experience with disposable needles) had difficulty attaching the needle. Three patients did not realize initially that they needed to screw the needle on. Two patients initially thought they had to do something with the end of the pen injector before they could attach the needle. One HCP and one patient took more time than other removing the inner cap.

2. Discarding priming/activation dose (n=2)

- i. Participant 27 and 50 (trained patients): Performed activation step before each regular dose. Participants forgot that activation step is only performed once resulting in on getting regular dose, but pen would not last 14 days.

3. Proper removal of needle (n=5)

- i. Five patients (four trained and one untrained), inexperienced with disposable needles): experienced minor needle-stick when recapping the needle to remove it. Two participants recapped at an angle, pushing the needle through the outer cap. Three pushed the needle through the outer cap. The Applicant attributed this to the fact that the 12 mm needle length was used in the study, which is greater than the standard size of 8 mm. In this study approximately 50% used the 8 mm needle length and no needle sticks were experienced.

Supplemental Validation Study

Table 15 – Results of scenario 2 (first dose – unpacking/activating pen-injector; delivery of first dose into skin pad), n=15

Step/task	Patient untrained group		
	Success with little/no effort (S)	Success with difficulties or effort (SD)	Failures (incorrect performance) or omission of the task (lack of performance) (F)
Safe removal of pen from packaging	S: 15 (100%)	0	0
Removal of pen cap	S: 15 (100%)	0	0
Attaching the needle and removing caps	S: 15 (100%)	0	0
Discard priming/activation dose	S: 12 (80%)	0	F: 3 (20%)
Inject first dose	S: 13 ^a (87%)	SD: 2 (13%)	0
Proper removal and disposal of needle	S: 15 (100%)	0	0

^a This includes the three participants who failed to discard the priming/activation dose (see previous step) it as a first dose.

In the re-validation, there were three failures which all occurred during the activation task and two close calls during the first dose injection. .

1. Failures in the re-validation study occurred during the “Discard priming/activation dose” task (n=3).
 - a. Participant 6 (untrained pen-naïve user): Failed to press injection button all the way in during activation step resulting in an injection of an incomplete first dosage. Patient stated he would have called the pharmacy to ask why the window did not turn white.
 - b. Participant 14 (untrained, experienced pen user): Failed to discard the activation fluid resulting in an injection of an incomplete first dosage. Patient stated that he never discards the activation step because it is a waste of medication.
 - c. Participant 15 (untrained): Failed to discard the activation fluid resulting in an injection of an incomplete first dosage. Participant skipped Section 2 and did not read the explanation of the activation step.
2. Success with difficulties or effort in the re-validation study occurred during the “Inject first dose” task (n=2).
 - a. Participant 1 discarded the activation step correctly, but did not continue to the injection step. Patient was distracted about wasting medication.
 - b. Participant 8 performed the activation step correctly, but could not remember whether she performed the activation step or whether to do it again. She looked at the plunger and realized she did and performed the injection step correctly.

Differentiation

There were no failures in differentiating between the 10 mcg per dose and 20 mcg per dose Lixisenatide pens for all participants (16 Health Care Professionals and 18 Patients).

Comprehension/Readability

The participants (15 type 2 DM patients) were able to find answers in the IFU in reasonable time.

One participant had some difficulties in answering the question if he could store the pen with a needle attached. He answered that he would ask his doctor about this question

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SARAH K VEE
03/22/2016

YELENA L MASLOV
03/23/2016

LUBNA A MERCHANT
03/23/2016

**REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 208471

Application Type: Original

Name of Drug/Dosage Form: lixisenatide injection

Applicant: Sanofi-Aventis U.S. LLC

Receipt Date: July 27, 2015

Goal Date: July 27, 2016

1. Regulatory History and Applicant's Main Proposals

Lixisenatide is a potent and selective DPP-4 resistant GLP-1 receptor agonist. Initially on December 20, 2012, Sanofi-Aventis submitted NDA 204961 application for lixisenatide as an adjunct to diet and exercise to improve glycemic control in the treatment of adults with Type 2 diabetes mellitus (T2DM). The sponsor withdrew this NDA application on September 11, 2013, in order to await the complete results of the ELIXA cardiovascular outcomes study rather than have the FDA review the interim data. The ELIXA study has been completed, and the sponsor has now submitted this data in the current application (NDA 208471).

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Selected Requirements of Prescribing Information

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)

Selected Requirements of Prescribing Information

• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- N/A** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A

Selected Requirements of Prescribing Information

15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES**
S 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES

Selected Requirements of Prescribing Information

22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

N/A 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- YES** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

N/A

Selected Requirements of Prescribing Information

34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- N/A** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARTIN L WHITE
10/07/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 208471		Efficacy Supplement Category: N/A <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: Established/Proper Name: Lixisenatide Dosage Form: subcutaneous Injection Strengths: 10 µg and 20 µg		
Applicant: Sanofi US Services Inc Agent for Applicant (if applicable):		
Date of Application: 7/27/2015 Date of Receipt: 7/27/2015 Date clock started after UN:		
PDUFA/BsUFA Goal Date: 7/27/2016		Action Goal Date (if different):
Filing Date: 9/25/2015		Date of Filing Meeting: 9/10/2015
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Lixisenatide is proposed to be indicated as an adjunct to diet and exercise to improve glycemic control in the treatment of adults with type 2 diabetes mellitus.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
The application will be a priority review if:	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"> • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) • The product is a Qualified Infectious Disease Product (QIDP) • A Tropical Disease Priority Review Voucher was submitted • A Pediatric Rare Disease Priority Review Voucher was submitted 	
Resubmission after withdrawal? <input checked="" type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input checked="" type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): IND 062724

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system? If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

cover letter, and annotated labeling). If yes , answer the bulleted questions below:					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input type="checkbox"/>		
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input type="checkbox"/>		
Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm					
If yes , please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity	YES	NO	NA	Comment	
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>			
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>					
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
If yes , # years requested: 5					
<i>Note: An applicant can receive exclusivity without requesting it;</i>					

<i>therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no , explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes , BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff :</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

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<i>forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<u>BPCA:</u> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

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If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format? ⁵	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has a review of the available pregnancy and lactation data been included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, specify consult(s) and date(s) sent: OPDP, CDRH, and DPMH, sent on 9.10.2015. OSI sent on 9.29.2015.</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date(s): December 19, 2007 and June 25, 2010	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): November 28, 2012 and June 08, 2015	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 10, 2015

BACKGROUND:

Lixisenatide is a potent and selective DPP-4 resistant GLP-1 receptor agonist. Initially on December 20, 2012, Sanofi-Aventis submitted an NDA application for lixisenatide (AVE0010) as an adjunct to diet and exercise to improve glycemic control in the treatment of adults with Type 2 diabetes mellitus (T2DM). The sponsor withdrew this NDA application on September 11, 2013 in order to await the complete results of the ELIXA cardiovascular outcomes study rather than have the FDA review the interim data. The ELIXA study has been completed, and the sponsor has now submitted this data in the current application (NDA 208471).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Martin White	Yes
	CPMS/TL:	Pamela Luccarelli	Yes
Cross-Discipline Team Leader (CDTL)	William (Bill) Chong		Yes
Division Director/Deputy	Jean-Marc Guettier		Yes
Office Director/Deputy	Curtis Rosebraugh		No
Clinical	Reviewer:	Andreea (Ondina) Lungu	Yes
	TL:	William (Bill) Chong	
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Pharmacology	Reviewer:	Sury Sista	Yes

	TL:	Manoj Khurana	Yes
• Genomics	Reviewer:	N/A	
• Pharmacometrics	Reviewer:	N/A	
Biostatistics	Reviewer:	Jiwei He	Yes
	TL:	Mark Rothmann	Yes

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Indra Antonipillai	Yes
	TL:	Dave Carlson	Yes
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC) Review Team:	ATL:	Danae Christodoulou	Yes
	RBPM:	Anika Lalmansingh	No
• Drug Substance	Reviewer:	Joseph Leginus	No
• Drug Product	Reviewer:	Ravi Kasliwal	No
• Process	Reviewer:	Yuesheng Ye	No
• Microbiology	Reviewer:	Maria Cruz-Fisher	No
• Facility	Reviewer:	Vipulchandra Dholakia	No
• Biopharmaceutics	Reviewer:	N/A	
• Immunogenicity	Reviewer:	N/A	
• Labeling (BLAs only)	Reviewer:	N/A	
• Other (e.g., Branch Chiefs, EA Reviewer)	Christopher Brown, CDRH Compliance		
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Twanda Scales	No
	TL:	Marcia Britt-Williams	No
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Charuni Shah	No
	TL:	Olga Salis	No
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Sarah Vee	Yes
	TL:	Yelena Maslov	Yes
OSE/DRISK (REMS)	Reviewer:	Amarilys Vega	No
	TL:	Naomi Redd	Yes
OSE/DPEI	Reviewer:	N/A	

	TL:	Patricia Bright	Yes
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:	N/A	
Bioresearch Monitoring (OSI)	Reviewer:	Cynthia Kleppinger	no
	TL:	Janice Pohlmen	yes
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers/disciplines			
<ul style="list-style-type: none"> • Safety Stats (Biometrics Division VII) 	Reviewer:	Yueqin Zhao	yes
	TL:	Mat Soukup	yes
OSE (DPV)	Reviewer:	Debra Ryan	yes
•	TL:	Christian Cao	yes
Other attendees	Bindi Ninki		Yes

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505 b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
---	--

<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments

<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

Comments:	
CLINICAL MICROBIOLOGY	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
CLINICAL PHARMACOLOGY	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
BIOSTATISTICS (DB II)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input checked="" type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u>	
<ul style="list-style-type: none"> Is the product an NME? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u>Environmental Assessment</u>	
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>If no, was a complete EA submitted?</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? If so, were the late submission components all submitted within 30 days? 	<p><input type="checkbox"/> N/A</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>

<ul style="list-style-type: none">• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none">• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Curtis Rosebraugh

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): January 5, 2015

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

1. Important dates

- Receipt date: July 27, 2015
- Site Selection Meeting: Sept 3, 2015
- Filing meeting: Sept 10, 2015
- 74 day letter: Oct 9, 2015
- Mid cycle Meeting: Jan 5, 2016
- Post-Mid-Cycle Meeting Communication with Applicant: Jan 14, 2016
- Complete primary review: April 2, 2016
- Wrap-up Meeting: June 8, 2016
- Complete secondary review: April 9, 2016
- Issue DR letters: April 16, 2016
- Send labeling to sponsor: April 8, 2016
- Labeling/PMR/PMC Discussion with Applicant: April 16, 2016
- CDTL review complete: June 15, 2016
- PeRC meeting: June 15, 2016
- Compile and Circulate Action Letter and Action Package: ~June 15, 2016
- Division Director Review of Action Package and Decision: ~June 15, 2016
- REMS finalized; DRISK review of REMS finalized: ~ no later than July 20, 2016
- ODE Review of Action Package and Decision: 0-3 weeks prior to action
- PDUFA goal date: July 27, 2016

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review</p>

ACTION ITEMS

<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRA completed: September 2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARTIN L WHITE
10/07/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Devices and Radiological Health

Office of Compliance, Division of Manufacturing and Quality

Respiratory, ENT, General Hospital, & Ophthalmic Devices Branch

DATE: September 22, 2015

TO: Suong Tran, PhD
OMPT/CDER/OPQ/ONDP/DNDPI/NDPBII, WO21 RM2518,
Suong.Tran@fda.hhs.gov

CC Office of combination products at combination@fda.gov

Through: Rakhi M. Dalal, Ph.D., Toxicologist Respiratory, Respiratory, ENT,
General Hospital and Ophthalmic Device Branch (REGO), Division
of Manufacturing Quality (DMQ), Office of Compliance (OC),
Center for Devices and Radiological Health (CDRH)

**Rakhi M.
Panguluri -S**

Digitally signed by Rakhi M. Panguluri -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300200210,
cn=Rakhi M. Panguluri -S
Date: 2015.09.23 17:19:58 -04'00'

From: Christopher J. Brown, Mechanical Engineer, REGO/DMQ,/OC/ CDR,
WO66-3428

Applicant: Establishment (Applicant):
Contact: David Faunce, Director
Sanofi-Aventis, US LLC
55 Corporate Drive
Bridgewater, NJ 08807
Phone: (908) 981-3538
Fax: (877) 332-5512
FEI: 3003596612

Establishment (Manufacturer)
Sanofi-Aventis Deutschland GmbH
Brüningstraße 50
Industriepark Höchst
65926 Frankfurt am Main, Germany
Phone: +49 0 69 305165
FEI: 3003195501

US Contact: N/A

Application #

NDA 208471

Product Name:

Lixisenatide pen-injector

Consult

1. CDER has requested:

Instructions:

- a. CDRH/OC to perform review of the application for deficiencies related to 21 CFR 820,
- b. CDER has requested that site appropriate to be inspected are identified: addressed in this review.

The Office of Compliance at CDRH received consult for NDA 208471, from CDER to review of the application for deficiencies related to 21 CFR 820, and evaluate NDA 208471 and identify the appropriate inspections site(s) for the combination product identified in the application.

Additionally, EIR for Sanofi-Aventis Deutschland GmbH, from 6/24/2013 to 7/02/2013 was consulted for this review.

Background

Sanofi-Aventis manufactures a Class II combination product consisting of a drug cartridge (Lixisenatide) inside of a medical device (injection pen). The product is intended for use by type 2 diabetes patients and is a once-daily prandial GLP-1 receptor antagonist (RA) for use in combination with basal insulin. According to Sanofi-Aventis, it is indicated for patients with type 2 diabetes mellitus when the following do not provide adequate glycemic control: diet and exercise (b) (4)

(b) (4)

The lixisenatide pen-injector is a disposable device combined with a cartridge that is used to dispense fixed doses of lixisenatide. It is a fully mechanical device, containing no electronic components. With regard to appearance and general handling characteristics, the lixisenatide pen-injector is similar to other disposable pen-injectors.

The lixisenatide pen-injector dispenses fourteen fixed doses of 0.2 mL. A dose is set by pulling out the button. The lixisenatide pen-injector is available for two different dosage strengths (Figure 1): 10 μ g and 20 μ g per 0.2 mL administration volume. The body and cap are provided in two different colors: green (10 μ g) and burgundy (20 μ g).



Concentration per dose (0.2 mL)	10 µg	20 µg
Concentration per mL	0.05 mg/mL	0.1 mg/mL
Color of pen	Green	Burgundy
Tactile feature on cap and button	Lines	Circles

Figure 1. Lixisenatide pen-injectors with different colors and tactile features

In addition, each strength bears differently shaped grip features on the button and on either side of the pen cap: lines (green pen) (Figure 2, Figure 3) and circles (burgundy pen). Apart from color and grip features, the geometry and function of each pen variant is identical, according to the firm.

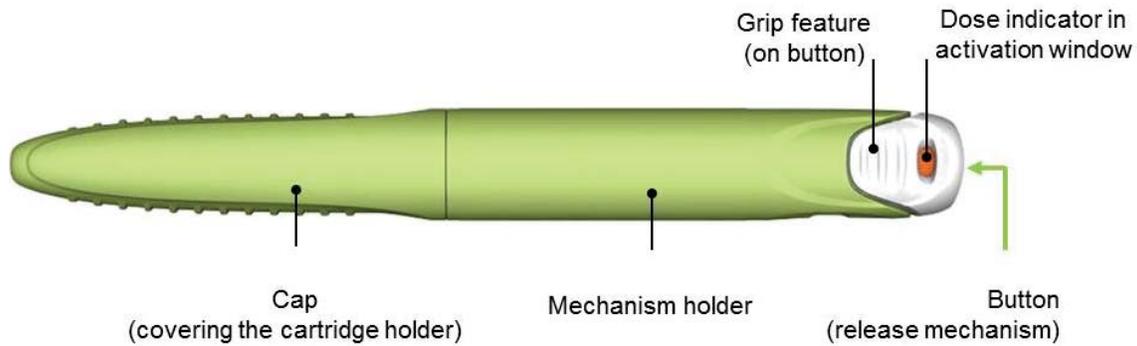


Figure 2. Lixisenatide pen-injector (closed cap – top view)

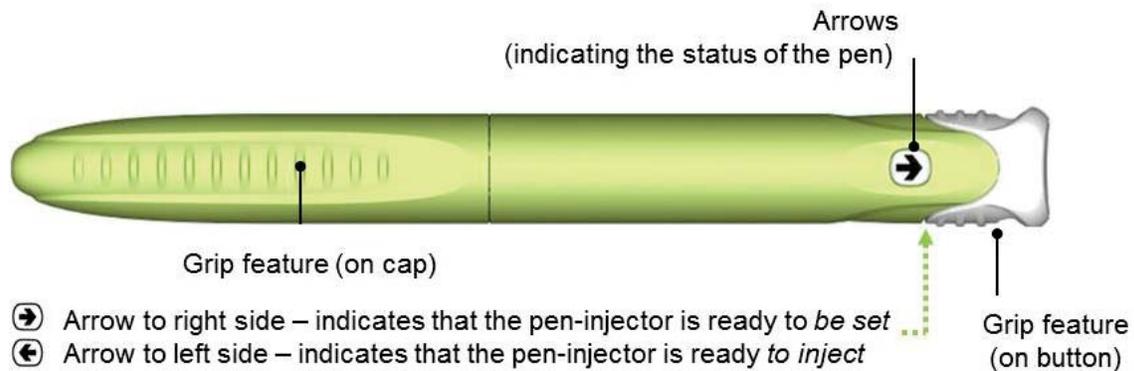


Figure 3. Lixisenatide pen-injector (closed cap – side view 1)

A new pen must be activated. Orange color on dose button window indicates a new pen which requires activation before injecting the first dose. White color on dose button window indicates an activated pen which is ready for injection.

Once a dose is set, the button cannot be returned to its starting position without dispensing any fluid. The dose is dispensed by pressing the button fully back into the body and subsequently maintaining pressure (with the needle in place within the patient) on the button for 2 seconds without retrieving the needle.

The cartridge contains the drug product to be dispensed by the device and which is (b) (4) assembled with the pen-injector. The cartridge consists of a (b) (4) tube, sealed at both ends with rubber components. The rubber component at the needle-end is the rubber seal. When the pen-injector is in use, the rubber seal is pierced by the needle to allow fluid to flow from the cartridge. The rubber component at the opposite end, the button-end, of the cartridge, is the plunger which is moved by the pen mechanism, forcing fluid through the needle. The cartridge provides a hermetic seal

around the medication, maintaining its sterility prior to use. Figure 4 shows the pen with the cap removed.

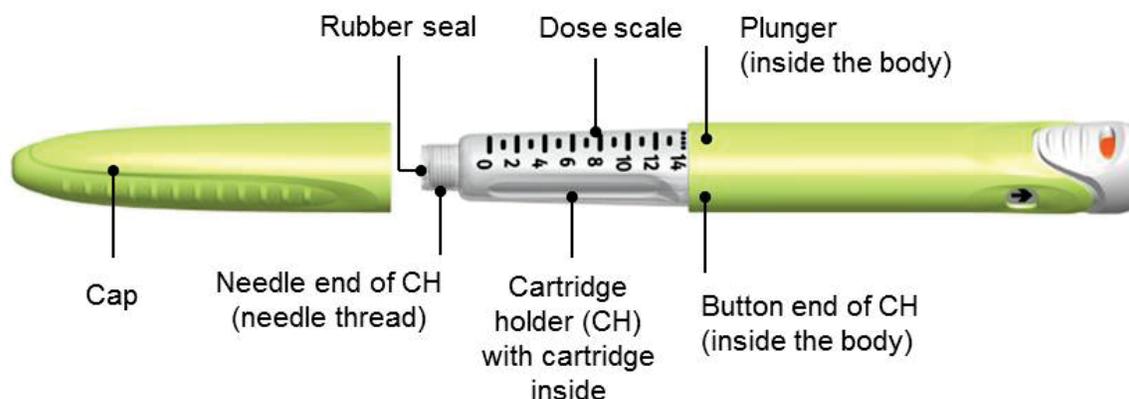


Figure 4. Lixisenatide pen-injector (cap taken off)

According to the firm, the lixisenatide pen-injector has no direct contact with the drug product. The cartridge (primary packaging) is filled (b) (4) and sealed with a rubber seal. The cartridge is inserted into the cartridge holder of the pen-injector, which, by itself, is not sterile. When a sterile pen needle is attached to the needle thread of the cartridge holder, only the sterile end of the needle punctures the rubber seal of the cartridge. The sterile drug solution is solitarily in contact with the sterile pen needle when the pen needle is attached to the pen-injector. When pen needle and rubber seal of the cartridge are connected, the "fluid pathway" is created. A dose is administered through the fluid pathway when the drug solution flows from the cartridge through the needle into the patient's body. No part of the pen-injector is in direct contact with the drug product solution or fluid pathway.

A needle must be attached to the thread on the cartridge-end of the device by screwing it onto the cartridge holder. An orange color appears in a window in the button before activation of the pen-injector (Figure 5 "New pen (not activated)"). When the activation step is performed, the color displayed within the window changes from orange to white (Figure 5 "Pen ready for injection (activated pen)"). The activation step comprises of loading the pen by pulling the injection button axially away from the needle in the direction of the arrow until the end stop is reached (Figure 6) and a "click" can be heard or felt.



New pen (not activated)



Pen ready for injection (activated pen)

Figure 5. - Activation window



Figure 6. Loading the pen-injector (dose setting)

When the button is fully extended, the arrow changes direction in the window located on the pen body and points towards the needle, indicating that the pen is ready for dispensing the dose. Once a dose is set, the button cannot be returned to its starting position without dispensing any fluid. The dose is dispensed by pressing the button fully back into the body until a tactile stop prevents any further movement and subsequently maintaining pressure (with the needle in place within the patient) on the button for 2 seconds without retrieve the needle. (b) (4)

. The subsequent dose can only be set when a dose has been completed.

Design Controls Review

The firm provided a copy of the FRA-SOP-02036 Design Control. This SOP describes the development process of a medical device and its components (including changes to marketed devices, when requested by a sponsor). The document outlines staff responsibilities and training. Further, it describes the design process, each stage in

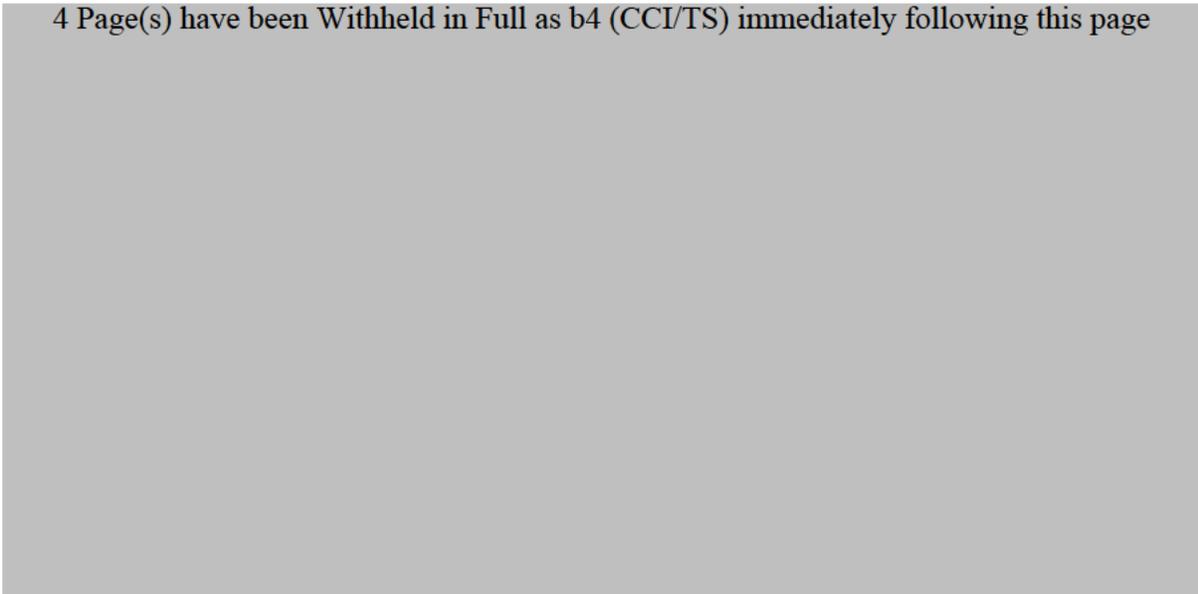
detail and lists the applicable SOPs for design transfer, design changes, design history file, human factors and engineering validation, verification, risk management, and design input and output.

The firm described the design process stages. The device design process at Sanofi following the (b) (4) (Figure 1) is organized in five different stages:



Figure 7. Sanofi Device Development Model

4 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page



The firm's submission is adequate. Their description of the documentation and requirements of their (b) (4) program appear to repeat the 21 CFR 820.50, requirement. But the firm provides sufficient documentation to substantiate the descriptions.

Regulatory history evaluation

Facility which may be subject to applicable Medical Device Regulations under 21 CFR part 820:

Establishment (Applicant):

Contact: David Faunce, Director

Sanofi-Aventis, US LLC

55 Corporate Drive

Bridgewater, NJ 08807

Phone: (908) 981-3538

Fax: (877) 332-5512

FEI: 3003596612

Role: Applicant – US Headquarters

Reviews:

I. Facility Inspection:

Inspection (b) (4)

Classified: NAI

This high priority CDER Sponsor inspection of Sanofi-Aventis U.S. LLC was initiated pursuant to an assignment memorandum dated 2/2/2015 from the Good Clinical Practice Assessment Branch (GCPAB), Division of Clinical Compliance Evaluation (DCCE), Office of Scientific Investigations (OSI), FACTS Assignment #11509997, OP ID # 7807659. Inspectional guidance was provided through CP 7348.810 (SPONSORS, CONTRACT RESEARCH ORGANIZATIONS AND MONITORS). (b) (4)

The previous inspection was a Post Marketing Adverse Drug Experience (PADE) inspection conducted from (b) (4) covering ADE reporting o (b) (4)

(b) (4). A Form FDA 483, Inspectional Observations, was issued at the conclusion of the inspection regarding the following: serious and unexpected adverse drug experiences were not always reported to the FDA within 15 calendar days and annual reports did not include the status of each post marketing study.

Since the facility has been inspected twice within the last two years, resources are limited and the manufacturer and applicant are part of the same firm, a pre-approval inspection of the applicant's facility is not required.

II. Facility Inspection:

Facility which may be subject to applicable Medical Device Regulations under 21 CFR part 820:

Establishment (Manufacturer)
Sanofi-Aventis Deutschland GmbH
Brüningstraße 50
Industriepark Höchst
65926 Frankfurt am Main, Germany
Phone: +49 0 69 305165
FEI: 3003195501

Reviews:

III. Facility Inspection:

(b) (4). Classified VAI. Unfortunately, there was no device CSO on this inspection, and the inspection was focused on drug product and API manufacturing. Specifically, the inspection covered (b) (4)

In general, as part of the Quality System coverage, they covered complaints, FARs and BPDRs, deviations/events/manufacturing investigations, changes, stability, batch record reviews, and various validations. Some of this review did overlap with what would be normally covered in a device inspection.

(b) (4). Classified NAI: This pre-approval and current GMP inspection of an API manufacturer was conducted per FACTS assignment #8945079 and in accordance with CP 7356.002F (API), 7356.002 (Drug Manufacturing Inspections) and 7346.832 (Pre-Approval Inspections). (b) (4)

(b) (4) This inspection covered Quality, Facility & Equipment, Materials, Production, and Laboratory Systems.

Since the facility has not been inspected for medical devices within the last two years, and the manufacturers responsibilities are critical a pre-approval inspection of the applicant's facility is required.

Note to CDER: CDRH, Office of Compliance recommends device inspection of the manufacturing facility of the combination product.

Deficiencies to be conveyed to the applicant

There are no outstanding deficiencies to be conveyed to the applicant.

CDRH Office of Compliance Recommendation

The Office of Compliance (OC) at CDRH has completed the evaluation of application - NDA 208471 and has the following recommendation:

Application Lixisenatide pen-injector approvability under the Medical Device Regulations should be delayed until the inspection of Site one Sanofi-Aventis Deutschland GmbH has been conducted and the site is deemed acceptable.

Christopher J. Brown -S
2015.09.23 15:47:08 -04'00'

Christopher J Brown, P.E., MLT (ASCP)

Prepared: Christopher J Brown: 09/23/2015

Reviewed: RDalal: 09/23/2015

CTS No.: ICC1500028

Application Number: NDA 208471

Inspectional guidance

CDRH recommends the inspection under the applicable Medical Device Regulations of:
Establishment (Manufacturer)
Sanofi-Aventis Deutschland GmbH
Brüningstraße 50
Industriepark Höchst
65926 Frankfurt am Main, Germany
Phone: +49 0 69 305165
FEI: 3003195501

- (1) A comprehensive baseline Level 2 inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30)

Additionally, evaluate the manufacturing activities associated with the manufacturing/assembly of the finished combination product, including in process and final acceptance activities. Detailed inspection guidance will be provided upon request. Questions regarding this consult should be referred to one of the following individuals:

Primary Contact

Christopher J Brown, P.E., MLT(ASCP)
Mechanical Engineer,
Respiratory, Ear/Nose/Throat, General Hospital, and Ophthalmic Devices Branch
(REGO), Division of Manufacturing Quality (DMQ)
Office of Compliance (OC), WO66 RM 2643A
Phone: 301-796-0380

Secondary Contacts (if Primary is unavailable and a timely answer is required)

Rakhi M. Dalal, Ph.D., Toxicologist
REGO/DMQ/OC
WO66 RM 3454
Phone: 301 796 6418

**THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM
DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL
INFORMATION**

There was no attachment contained within this review

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANIKA A LALMANSINGH

09/28/2015

Uploaded on behalf of Christopher J. Brown.