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RESEARCH**

*APPLICATION NUMBER:*

**208471Orig1s000**

**OFFICE DIRECTOR MEMO**

## Office Deputy Director Decisional Memo

<b>Date</b>	July 27, 2016
<b>From</b>	Mary Thanh Hai Parks, M.D.
<b>Subject</b>	Office Deputy Director Decisional Memo
<b>NDA/BLA #</b>	208471
<b>Supplement #</b>	
<b>Applicant Name</b>	Sanofi Aventis
<b>Date of Submission</b>	July 27, 2015
<b>PDUFA Goal Date</b>	July 27, 2016
<b>Proprietary Name / Established (USAN) Name</b>	Adlyxin (lixisenatide)
<b>Dosage Forms / Strength</b>	50 mcg/mL in 3mL pre-filled pen for 14 pre-set doses of 10 mcg each 100 mcg/mL in 3mL pre-filled pen for 14 pre-set doses of 20 mcg each
<b>Applicant Proposed Indication(s)/Populations</b>	As an adjunct to diet and exercise to improve glycemic control in adults with T2DM
<b>Action:</b>	Approval
<b>Approved Indication(s)/Populations (if applicable)</b>	As an adjunct to diet and exercise to improve glycemic control in adults with T2DM

# 1. Benefit-Risk Assessment

## Benefit-Risk Summary and Assessment

Lixisenatide is a short-acting GLP-1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The recommended dosing instructions are lixisenatide 10 ug once daily for two weeks then increase to 20 mcg once daily. Improved glycemic control, as determined by reductions in HbA1c, has been established to reduce long-term microvascular complications in T2DM and has been an accepted surrogate for approval of anti-diabetic agents.

There are currently 5 other marketed GLP-1 receptor agonists in the United States for the same indication. The clinical development program for lixisenatide is similar to these other therapies and establishes the effectiveness of the lixisenatide for improving glycemic control relative to placebo as monotherapy (~0.5% HbA1c reduction) and in combination with a variety of anti-diabetic therapies (range ~ -0.3 to -0.9% HbA1c reduction). Active-controlled trials comparing lixisenatide to several other available anti-diabetic therapies show non-inferiority to these comparators. However, one of these trials also showed that lixisenatide 20 ug once daily was inferior to exenatide 10 ug bid, a marketed short-acting GLP-1 receptor agonist. This finding doesn't challenge the inherent efficacy of lixisenatide established in the placebo-controlled trials. Inferiority to another GLP-1 receptor agonist also does not challenge approval as there are many marketed products within an established therapeutic class that show differences in efficacy.<sup>1,2</sup>

The safety profile of lixisenatide was evaluated in a very large controlled program. Relative to other marketed GLP-1 receptor agonists, this NDA contained a larger patient exposure database because it included a completed cardiovascular outcomes trial (CVOT). In addition, based on knowledge of certain class safety findings, this program included prospective assessments of adverse events of special interest. Overall, the most common adverse events of lixisenatide are gastrointestinal in nature (e.g., vomiting, nausea, abdominal pain) which are also described in labeling of all available GLP-1 agonists. The CVOT showed no evidence of excess risk for heart attacks, stroke or cardiovascular death. In addition, rodent carcinogenicity studies established a large margin of safety for risk of C-cell hyperplasia and tumors, a concern observed thus far with only the long-acting GLP-1 receptor agonists.

<sup>1</sup> USPI for Victoza includes data showing statistically significant reductions in HbA1c with liraglutide 1.8 mg compared to exenatide 10 mcg bid.  
[http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label\\_ApprovalHistory#labelinfo](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo)

<sup>2</sup> USPI for Crestor includes data showing greater LDL-lowering across dose ranges of rosuvastatin compared to atorvastatin, simvastatin, and pravastatin.  
[http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label\\_ApprovalHistory#labelinfo](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo)

Adjudicated cases of anaphylaxis occurred in more patients treated with lixisenatide (n=16, 0.2%) than placebo (n=5, 0.1%). Anaphylaxis, angioedema, and Stevens-Johnson syndrome have been reported with other marketed GLP-1 receptor agonists hence this is considered a class safety finding. However, these events have only been observed post-marketing not in the pre-marketing application of these currently marketed GLP-1 receptor agonists. It is unclear if the large pre-market exposure and targeted adjudication in the lixisenatide program enabled detection in this stage of development or if there is a difference in risk for anaphylaxis.

Treatment with lixisenatide resulted in a high rate of developing anti-drug antibodies (ADA); approximately 70% of patients receiving treatment beyond 24 weeks developed ADAs. It is not known if these ADAs are neutralizing; however, in a small number of patients (n=45) who had high concentrations of ADAs, glycemic efficacy was markedly attenuated (-0.16% HbA1c). Given the close homology to native GLP-1 and glucagon, it is also not clear if these ADAs may cross-react with endogenous hormones of glucose metabolism. Although there were more injection site reactions associated with ADA positivity, there were also some cases in those who were ADA-negative and of the overall number of patients with ADAs, the majority did not have a hypersensitivity reaction. ADAs were also observed with currently marketed GLP-1 receptor agonists in their clinical development program although at much lower rates.

In conclusion, the benefit of lixisenatide as a glucose-lowering agent was established in this NDA. Its safety profile was evaluated in the largest pre-market program for this class to date and showed similar class finding effects. Possible differences to available marketed GLP-1 receptor agonists include a higher percentage of patients developing ADAs and reports of anaphylaxis seen in clinical trials. None of these findings preclude approval as labeling will include these findings and such disclosure is intended to educate and inform prescribers as they select from the armamentarium of available diabetes therapies for their patients' needs. In addition, required postmarketing studies will continue to inform us of the benefit-risk profile of lixisenatide.

<b>Dimension</b>	<b>Evidence and Uncertainties</b>	<b>Conclusions and Reasons</b>
<b>Analysis of Condition</b>	<p>Type 2 diabetes mellitus is a chronic disease of dysregulated glucose metabolism affecting ~29 million Americans. Patients present with hyperglycemia which if severe can result in symptoms of blurred vision, polyuria, polydipsia, and weight loss. Long-term complications of diabetes include microvascular and macrovascular disease. Several large controlled trials have established that improved glycemic control based on reducing HbA1c reduce the risk of microvascular complications. Reductions in risk of macrovascular complications with improved glycemic control has not been fully established</p>	<p>This is a highly prevalent condition which is associated with short-term acute symptoms from hyperglycemia and long-term complications that are serious, debilitating and increase mortality and morbidity of these patients.</p>
<b>Current Treatment Options</b>	<p>There are 12 classes of anti-diabetic therapies. Lixisenatide will be the 6<sup>th</sup> in the class of GLP-1 receptor agonists. Glycemic control in T2DM often requires multiple therapies over time and response to therapies are variable between individual patients.</p>	<p>While there are many available therapies, patients often require multiple drug regimens and selection of treatment requires individualization based on patient response, underlying co-morbidities and concomitant medications.</p>
<b>Benefit</b>	<p>Data from 9 placebo-controlled trials demonstrated statistically significant reductions in HbA1c when lixisenatide 20 mcg once daily was administered as monotherapy or in combination with a variety of anti-diabetic agents. Active controlled trials demonstrated non-inferiority to exenatide, insulin glulisine, and sitagliptin; however, lixisenatide was also inferior to exenatide and glulisine tid.</p> <p>Glycemic control, as determined through reductions in HbA1c, has been established to reduce the risk of microvascular complications.</p>	<p>Lixisenatide is an effective glucose lowering agent. It will be the 6<sup>th</sup> GLP-1 receptor agonist to be approved. Although it does not appear to show an efficacy advantage over other approved GLP-1 receptor agonists this is not a requirement for approval.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<b>Risk</b>	<p>The most common adverse events are gastrointestinal in nature. Anaphylaxis and hypersensitivity reactions were observed in the clinical trials.</p> <p>There was a high rate of anti-drug antibody formation and in the small percentage of patients with high concentration of antibodies, there may be some attenuation of efficacy. Unclear if these antibodies are neutralizing or if cross-reactivity with endogenous GLP-1 may contribute to this observation.</p> <p>Completed CV safety trial did not reveal a cardiovascular safety concern.</p>	<p>Safety findings in application are typical of other drugs in this class. Anaphylaxis was observed in clinical trials whereas this adverse event was observed postmarketing setting with other approved products. This may be the result of a larger clinical database for lixisenatide and a prospective assessment for this risk. While more patients with anaphylaxis/hypersensitivity reactions were anti-drug antibody positive, the number of events was small and a large percentage of patients who were antibody positive did not have such reactions.</p>
<b>Risk Management</b>	<p>No REMS is being proposed</p> <p>PMRs include development of validated assays for neutralizing Abs and cross-reactivity of anti-drug antibodies with endogenous GLP-1 and glucagon.</p>	<p>The risks identified in this NDA are not unlike others in the drug class. Proposal to manage risks through labeling is appropriate.</p>

## 2. Further discussion to support regulatory action

### Background

This application is for lixisenatide (Adlyxin), 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 (T2DM). Lixisenatide is a synthetic peptide of 44 amino acids developed based off of exendin-4, a hormone found in the saliva of the Gila monster (*Heloderma suspectum*) which has similar biologic activity to human GLP-1.

GLP-1 is an incretin hormone that increases insulin secretion in response to an ingested meal. Unlike other anti-diabetic therapies, which control hyperglycemia through stimulation of insulin release from the pancreas (e.g. sulfonylureas or glinides), incretin-based therapies control hyperglycemia through a glucose-dependent manner thereby mitigating the risk of hypoglycemia. Because human GLP-1 is rapidly degraded by the serine protease, dipeptidyl peptidase IV (DPPIV), it has limited clinical use. Lixisenatide has a high degree of homology with the first 12 amino acids of human GLP-1 but it has been modified to have six lysine residues added to the C-terminus which makes it less susceptible to physiologic degradation by DPPIV. This modification to lixisenatide extends its half-life to approximately 2-4 hrs, similar to Byetta (exenatide), another marketed GLP-1 receptor agonist with a terminal half-life of approximately 2.4 hrs.

There are currently five marketed GLP-1 receptor agonists for the treatment of T2DM: Byetta (exenatide), Victoza (liraglutide), Tanzeum (albiglutide), Trulicity (dulaglutide), and Bydureon (exenatide long-acting). The clinical development program to establish glycemic efficacy for lixisenatide is similar to these other approved GLP-1 receptor agonists. In addition, lixisenatide initiated a cardiovascular outcomes trial (CVOT) during its IND stage of development to address the FDA's 2008 Guidance to Industry for assessing cardiovascular risk. This trial is called the ELIXA trial and the NDA for lixisenatide was initially submitted to FDA in 2013 which included the interim results of the ELIXA trial. As described in other FDA reviews, this NDA was withdrawn by Sanofi given concerns over a public discussion of the interim data of this ongoing CVOT. This resubmission now includes the completed results of ELIXA.

Reviews from all Centers, Offices, and Divisions contributing to the review of this NDA recommend approval. I concur with this recommendation and my memo will only highlight key findings, particularly those considered unique to lixisenatide and relevant for labeling.

### Product Quality and Clinical Microbiology

Please see CMC and CDRH (device) reviews. No deficiencies were identified in the drug substance, drug product or their manufacturing to preclude approval.

### Nonclinical Pharmacology/Toxicology

Please see the reviews of Drs. Brian Hummer, Feleke Eschete, Karen Davis Bruno and Todd Bourcier. Pharmacology and toxicology reviewers recommend approval of this NDA.

In 2009 there was extensive public discussion at the advisory committee meeting for the long-acting GLP-1 receptor agonist, liraglutide on risk of thyroid c-cell neoplasm in humans based on rodent carcinogenicity studies showing an increased risk of C-cell hyperplasia at doses similar to human clinical exposures. This safety concern resulted in a boxed warning describing the animal findings and a contraindication for use in patients with a personal or family history of medullary thyroid cancer or Multiple Endocrine Neoplasia 2 syndrome. The product label of liraglutide also included a Limitations of Use statement recommending against its use as first line therapy for T2DM in patients failing diet and exercise. The product was approved with a Risk Evaluation and Mitigations Strategy (REMS) and several post-marketing required studies. At that time, review of the nonclinical evidence for the short-acting GLP-1 receptor agonist, Byetta (exenatide), did not raise a similar concern. Since 2009, all long-acting GLP-1 receptor agonists have carried labeling as liraglutide. Byetta's label does not carry a similar label to the long-acting GLP-1 receptor agonists.

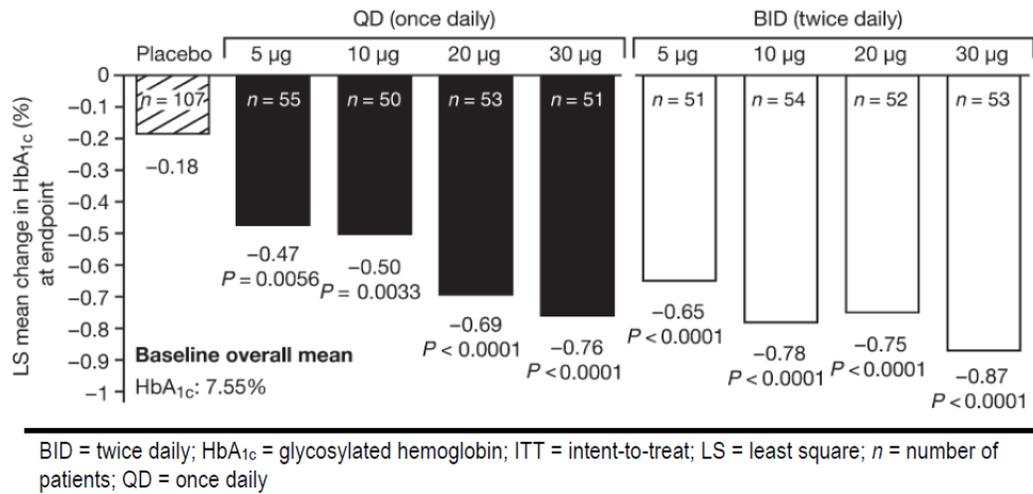
The rodent carcinogenicity studies for lixisenatide showed development of C-cell tumors at higher exposures than expected with clinical dosing of 20 ug once daily (approximately 272x and 5000x higher in male and female mice, respectively). Pharmacology/toxicology reviewers recommend labeling similar to the short-acting GLP-1 receptor agonist.

### **Clinical Pharmacology**

See FDA's Office of Clinical Pharmacology review authored by Drs. Sista, Jain, and Mehrota dated April 8, 2016.

Dose selection was based on one Phase 2, 13-week dose/exposure response study. This study evaluated qd (5-30 ug) and bid (5-30 ug) dosing. There was a clear dose-response relationship for efficacy and safety. The bid dosing regimen in this 13-week study demonstrates a greater reduction in HbA1c than observed with qd dosing. Gastrointestinal AEs were also observed at a lower rate with the bid dosing than qd in this 13-week study.

Figure 1. Mean Change in HbA1c from Phase 2 Dose-Response Study (source: Applicant submission)



Despite these differences between bid and qd dosing, the applicant selected the 20 mg qd dosing regimen for Phase 3 studies. The clinical pharmacology review (Section 1.3.3) puts forward the rationale for once-daily dosing. Among these I would agree that the effect of delayed gastric emptying on certain co-administered drugs may be more problematic for a twice-daily lixisenatide dosing regimen although this would not be applicable to all patients. While the once-daily regimen would align this product in the market with liraglutide which is dosed once-daily, Sanofi's selection of a once-daily regimen for lixisenatide may have also contributed to its inferior efficacy compared to exenatide 10 mg bid observed in one of the Phase 3 trials.

Other notable findings and/or recommendations from the Clinical Pharmacology review include:

- No substantial QT prolongation at therapeutic dose and supra-therapeutic dose (30 ug bid) exposures
- Restrict dosing to 10 ug qd in patients with severe renal impairment
- No notable difference in bioavailability across injections in abdomen, thigh, or arm
- No expected drug-drug interactions although timing of dosing of certain drugs apart from lixisenatide dosing is recommend due to delayed gastric emptying

### Clinical/Statistical – Efficacy

Please see reviews of Drs. Wei Liu dated August 19, 2013, and Dr. Jiwei He dated March 21, 2016.

The efficacy of lixisenatide on reducing HbA1c was established in 9 placebo-controlled trials including one monotherapy trial and 8 add-on trials in which lixisenatide was added onto a variety of anti-diabetic regimens including metformin, sulfonylureas, pioglitazone, basal

insulin or some combination of all of these available therapies. With exception for the monotherapy trial, the placebo-controlled trials were of 24 weeks duration for determination of efficacy on glycemic control. The following table adapted from Dr. Liu's review summarizes the primary efficacy findings from the 9 placebo-controlled trials.

**Table 1. Effect of Lixisenatide on HbA1c in Pbo-Controlled Trials (adapted from Dr. Liu's review)**

Study (Treatment)	Mean Baseline HbA1c	Mean Change from Baseline	Lixi-Pbo (95% CI)
<b>Monotherapy</b>			
<b>EFC6018</b>			
Lixi 2-step increase	7.97	-0.73	-0.54 (-0.78, -0.30)
Lixi 1-step increase	8.06	-0.85	-0.66 (-0.90, -0.42)
Placebo	8.07	-0.19	
<b>Add-on to Metformin</b>			
<b>EFC6014</b>			
Lixi, am	8.07	-0.87	-0.48 (-0.66, -0.31)
Lixi, pm	8.07	-0.75	-0.37 (-0.54, -0.19)
Placebo	8.02	-0.38	
<b>EFC10743</b>			
Lixi 2-step increase	8.12	-0.83	-0.41 (-0.58, -0.23)
Lixi 1-step increase	7.99	-0.92	-0.49 (-0.67, -0.32)
Placebo	8.03	-0.42	
<b>Add-on to SU (or SU + Metformin)</b>			
<b>EFC6015</b>			
Lixi	8.28	-0.85	-0.74 (-0.87, -0.62)
Placebo	8.22	-0.10	
<b>Add-on to Pioglitazone (or Pio + Metformin)</b>			
<b>EFC6017</b>			
Lixi	8.08	-0.90	-0.56 (-0.73, -0.39)
Placebo	8.05	-0.34	
<b>Add-on to Basal Insulin (or Basal Insulin + Metformin)</b>			
<b>EFC6016</b>			
Lixi	8.39	-0.74	-0.36 (-0.55, -0.17)
Placebo	8.38	-0.38	
<b>Add-on to Insulin Glargine + Metformin (or Insulin Glargine + Metformin + TZD)</b>			
<b>EFC10781</b>			
Lixi	7.56	-0.71	-0.32 (-0.46, -0.17)
Placebo	7.60	-0.40	
<b>Add-on to Basal Insulin (or Basal Insulin + SU)</b>			
<b>EFC10887</b>			
Lixi	8.53	-0.77	-0.88 (-1.12, -0.65)
Placebo	8.53	0.11	
<b>Add-on to Metformin (or Metformin + SU)</b>			
<b>EFC11321</b>			
Lixi	7.95	-0.83	-0.36 (-0.55, -0.16)
Placebo	7.83	-0.47	

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Efficacy of lixisenatide was also compared to another GLP-1 analogue (exenatide), the rapid-acting insulin (insulin glulisine), and the DPP4-inhibitor, sitagliptin. In these active-controlled trials, lixisenatide was shown to be non-inferior to the active comparators

Study EFC6019 was a 24-week, open-label trial comparing lixisenatide 20 mg qd to exenatide 10 mg bid as add-on to metformin on HbA1c reduction. Lixisenatide 20 mg qd was non-inferior to exenatide 10 mg bid as the upper bound of the 95% CI was below 0.4%; however, lixisenatide was also inferior to exenatide. This observation was consistent with both the MMRM and completer's analyses. Dr. Liu also evaluated efficacy at later time points and non-inferiority was no longer observed at timepoints beyond Week 24.

**Table 2. Efficacy Results from Study EFC6019 (adapted from Dr. Liu's review)**

	Lixisenatide 20 mg qd	Exenatide 10 mg bid	Lixi-Exen, (95% CI)
Baseline Mean HbA1c	7.97	7.96	
Adj. Mean Chg from Baseline			
LOCF	-0.79	-0.96	0.17 (0.03, 0.30), p=0.01
MMRM	-0.80	-0.95	0.15 (0.02, 0.27), p=0.02
Completers (at Wk 24)	-0.84	-1.02	0.18 (0.04, 0.32), p=0.01
Observed (at Wk 52)	-0.77	-1.05	0.27 (0.13, 0.42), p=0.0002
Observed (at Wk 76)	-0.87	-1.17	0.29 (0.12, 0.46), p=0.0008

Study EFC12626 was a 26-week, open-label trial comparing lixisenatide 20 mg qd to the prandial insulin glulisine qd or insulin glulisine tid in patients with T2DM with inadequate control on glargine +/- metformin. The primary objectives were to demonstrate non-inferiority of lixisenatide to the two glulisine treatment arms and superiority on body weight changes. Dr. He's review summarizes the testing procedures for showing NI and superiority. Lixisenatide was non-inferior to insulin glulisine qd and tid for HbA1c reduction. It was not superior to either insulin treatment regimens and in fact, was inferior to insulin glulisine tid. This observation was consistent across the different analyses.

**Table 3. Efficacy Results from Study EFC12626 (adapted from Dr. Liu's review)**

	Lixisenatide N=292	Insulin Glulisine QD N=292	Insulin Glulisine TID N=295
LS mean change in HbA1c from baseline	-0.63	-0.58	-0.84
LS mean difference (95% CI) of lixisenatide vs insulin glulisine	---	-0.05 (-0.17, 0.064)	+0.21 (0.095, 0.328)

Lixisenatide was superior to both insulin glulisine treatment arms for mean change in body weight from baseline.

### Conclusions on Efficacy

The applicant was able to establish the effectiveness of lixisenatide for glycemic control of type 2 diabetes from the placebo-controlled trials. While not required for approval, the active-controlled trials provide useful information on comparative effectiveness to other anti-

diabetics. The head-to-head comparison to exenatide bid merits inclusion in labeling to inform prescribers choosing from among the available GLP-1 receptor agonists, especially the statistically inferior effect of lixisenatide for glycemic control over exenatide 10 mg bid. The inferior efficacy may be the result of Sanofi's decision to develop this short-acting GLP-1 agonist as a once-daily regimen despite pharmacokinetic data and a Phase 2 trial suggesting better efficacy with twice-daily dosing.

## **Safety**

The pre-marketing safety database for lixisenatide included 20 completed Phase 2/3 studies with over 10,000 patient-yrs of exposure to lixisenatide and a median duration of treatment of 526 days. The CV outcomes trial, ELIXA, contributed approximately half of the exposure data. This pre-marketing safety exposure is larger than any currently marketed GLP-1 agonist.

The most common adverse events associated with the GLP-1 agonists involve the gastrointestinal system with nausea, vomiting, diarrhea, and abdominal pain among the symptoms reported in clinical trials. Lixisenatide is no exception with 40% of patients in the placebo-controlled trials reporting a GI adverse event versus 18% on placebo.

In addition, the following adverse events are listed under the Warnings and Precautions (W and P) section for all the currently marketed long-acting GLP-1 agonists: thyroid C-cell tumors in animals, pancreatitis, hypoglycemia when used with insulin or an insulin secretagogue, hypersensitivity reactions, and renal impairment. Dr. Balakrishnan has done an exhaustive safety review of this NDA and a similar description of all other AEs (except for thyroid C-cell tumors) under the W and P section of GLP-1 agonists will be included in the W and P section of lixisenatide. Safety findings related to hypersensitivity reactions including anaphylaxis and immunogenicity with development of anti-drug antibodies will have greater emphasis in labeling and I will summarize these findings more below.

### Hypersensitivity Reactions and Anaphylaxis

Please see consults from Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) dated August 26, 2013 and April 6, 2016.

The applicant established an Allergic Reaction Adjudication Committee (ARAC) to evaluate potential hypersensitivity reactions in a prospective fashion. The selection of cases and adjudication process have been described in the consult from DPARP. In the Phase 2/3 program there were 16 cases of anaphylaxis identified in lixisenatide-treated patients; one additional case was reported in a Phase 1 study. In contrast, there were 5 cases reported in the placebo group. The cases have been reviewed by FDA allergists/immunologists and accounting for other triggers/inciting agents that more likely caused anaphylaxis, a calculated frequency of 0.1% for lixisenatide-associated anaphylaxis was observed. All cases in placebo had an identifiable cause for anaphylaxis.

Anaphylaxis, Stevens-Johnson syndrome, and angioedema have been reported with all currently marketed GLP-1 agonists although these have occurred in the postmarketing setting. Lixisenatide is different in that cases have been reported pre-marketing; however, a larger

clinical trial exposure and targeted adjudication also distinguishes this program from the currently marketed products and it is conceivable that this may have contributed in identifying cases in the pre-market setting.

The applicant provided comparative data to other currently marketed GLP-1 agonists to conclude no difference in risk of anaphylaxis between lixisenatide and these marketed compounds; however, such analyses compared post-marketing reports to cases identified premarketing and cannot be considered reliable for evaluating risk across the class of drugs.

In conclusion, randomized controlled data clearly show a greater risk of anaphylaxis associated with lixisenatide than other non-GLP-1 comparators. A greater risk relative to marketed GLP-1 agonists cannot be determined with the available data. In contrast to currently marketed GLP-1 agonists, labeling for lixisenatide will specify that this adverse event was identified in clinical trials.

#### Immunogenicity and Anti-drug Antibodies (ADA)

Data from 9 placebo-controlled trials reveal that 70% of patients developed anti-drug antibodies after 24 weeks of treatment. In those patients evaluated after Week 100 of treatment, 70.2% were ADA positive. A meta-analysis of several controlled trials suggest diminished efficacy with high concentration of ADAs. From Table 2 below submitted by the applicant, in a small percentage of patients who had ADA concentrations > 100 nmol/L, HbA1c reduction was markedly diminished (-0.16) in comparison to the ADA-negative patients or those with concentrations < LLOQ (-0.83 to -0.88).

**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 <sup>b</sup>	SE <sup>b</sup>	95% C.I. <sup>b</sup>
Anti-lixisenatide antibody status <sup>a</sup>				
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 <sup>c</sup>				
Antibody negative	621/1890 <sup>d</sup> ( 32.9%)			
<LLOQ	854/1890 <sup>d</sup> ( 45.2%)	-0.88	0.043	(-0.963 to -0.796)
Total antibody negative or <LLOQ	1475/1890 <sup>d</sup> ( 78.0%)	-0.86	0.035	(-0.930 to -0.795)
≥ LLOQ	415/1890 <sup>d</sup> ( 22.0%)	-0.63	0.050	(-0.732 to -0.534)
≤100 nmol/L	370/1890 <sup>d</sup> ( 19.6%)	-0.64	0.057	(-0.751 to -0.528)
>100 nmol/L	45/1890 <sup>d</sup> ( 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.

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

<sup>b</sup> 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.

<sup>c</sup> Based on patients with HbA1c and anti-lixisenatide antibody concentration collected on the same date.

<sup>d</sup> 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.

Given the homology of lixisenatide to human GLP-1 and glucagon, it is unclear if this diminished efficacy is the result of neutralizing antibodies (nAbs) or cross-reactivity with endogenous GLP-1 and the applicant will be required to develop validated assays for nAbs and cross-reactivity as postmarketing studies. The presence of ADAs and risk of hypersensitivity reactions was also evaluated and while more patients who had injection site reactions were ADA-positive (5.6%) there were also events occurring in ADA-negative patients (2.3%) and the majority of ADA-positive patients did not experience a hypersensitivity reaction or injection site reaction.

The applicant provided follow-up antibody data in ADA-positive patients who discontinued treatment and it is suggestive that positivity status decreases over time; however, the sample size contributing to this observation was small (n=54).

The review team has concluded that the immunogenicity findings do not preclude approval and that this potential efficacy and safety concern will be included in labeling. I am in agreement with the review team but do note that the development of anti-drug antibody appears higher with this product than observed with other GLP-1 agonists. Dr. Balakrishnan summarized the following from the USPI of these approved products.

**Table 32: Antidrug Antibodies- Approved GLP-1 receptor agonists**

Approved GLP-1 receptor agonists	Reported incidence of ADA formation <sup>1</sup>
Exenatide	20-38%
Liraglutide	8.6%
Exenatide LAR	49%
Albiglutide	5.5%
Dulaglutide	1.6%

1. Based on approved USPI's

While assays and data collection are different across programs and no comparative safety can be made across this drug class, the label for lixisenatide should clearly note the high rate of ADA development and its potential to impact efficacy.

#### Cardiovascular Safety

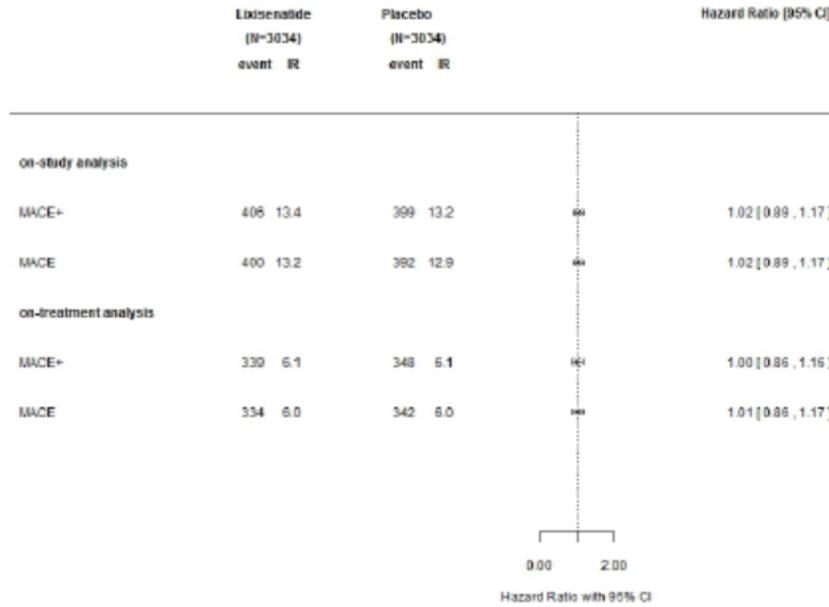
Please see Statistical Review authored by Drs. Zhao, Soukup, and Levenson dated April 7, 2016.

The ELIXA trial was a cardiovascular outcomes trial comparing lixisenatide to placebo as add-on to standard of care diabetes therapy. The primary objective was to exclude an 30% excess CV risk based on a primary analysis of time to first event of the composite of MACE+ (CV death, nonfatal MI, nonfatal stroke, and hospitalization for unstable angina). The composite of MACE (CV death, nonfatal MI, and nonfatal stroke) was also evaluated. Unlike other GLP-1 agonists currently marketed, lixisenatide's pre-market NDA contains the completed CVOT to address the FDA's 2008 Guidance entitled, "Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes." The applicant previously submitted the interim results of ELIXA under NDA 204961 but withdrew that application citing concerns over maintaining integrity of an ongoing trial being presented before a public advisory committee meeting.

ELIXA randomized 6068 patients with T2DM at high CV risk based on a qualifying ACS event with ST-segment elevation MI making up the majority of events. The median age of this study population was 60 yrs. The median duration of treatment was approximately 23 months and follow-up was 26 months. At the end of the trial, 805 patients experienced a MACE+ (399 on placebo and 406 on lixisenatide) yielding a HR of 1.02 with accompanying 95% CI of 0.89-1.17. An ITT analysis of MACE yielded a similar finding (HR 1.02; 95% CI: 0.89-1.18). Both excluded a 30% excess risk and sensitivity analyses and analyses of components of the composite endpoints support a conclusion that ELIXA provided reassuring CV safety data meeting the expectations of the FDA 2008 CV guidance.

(source: Dr. Zhao's review)

**Figure 1: Hazard Ratios of the MACE+ and MACE Endpoint (On-study and On-treatment Analysis)**



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Evaluation of the individual components contributing to the primary composite showed no adverse signal for any of these events.

**Table 4. Findings on components of primary endpoint in ELIXA (adapted from Dr. Zhao's review)**

	Placebo N=3,034	Lixisenatide N=3,034
CV death	93 (3.1%)	88 (2.9%)
Nonfatal MI	247 (8.1%)	255 (8.4%)
Nonfatal stroke	49 (1.6%)	54 (1.8%)
Hospitalization for unstable angina	10 (0.3%)	9 (0.3%)

**Advisory Committee Meeting**

This NDA was presented along with the NDA for the lixisenatide-glargine fixed-ratio combination product on May 25, 2016, to the Endocrine and Metabolism Drugs Advisory Committee. The meeting focused primarily on the combination of titratable insulin combined with non-titratable lixisenatide although high level findings from the lixisenatide program and the ELIXA trial were presented. Several members noted the different efficacy to other GLP-1 agonists and the higher rate of developing anti-drug antibodies than observed with other GLP-1 programs but overall when asked to discuss any issues related to the efficacy and safety of lixisenatide for the treatment of type 2 diabetes mellitus and whether the issues would preclude approval of lixisenatide, no members raised concerns over the approvability of lixisenatide.

**Pediatrics**

Pediatric studies will be required under PREA.

**Other Relevant Regulatory Issues**

None.

**Labeling**

Please see attached labeling with action letter. With exception for description of the high rate of anti-drug antibody development, anaphylaxis in clinical trials, and the active comparator trials demonstrating inferiority to exenatide 10 mg bid, this product label is similar to the other marketed GLP-1 receptor agonists.

**Risk Evaluation and Mitigation Strategies**

None required.

**Postmarketing Requirements and Commitments**

Please see Dr. Chong's memo. In addition to studies required under PREA, the applicant will be required to further assess for neutralizing antibodies and antibodies cross-reacting with endogenous GLP-1 and glucagon.

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/s/  
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MARY H PARKS  
07/27/2016