

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	208471
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Reviewer Name(s)	Amarilys Vega, MD, MPH
DRISK Team Leader	Naomi Redd, Pharm.D
Division Director	Cynthia LaCivita, Pharm.D
Review Completion Date	July 19, 2016
Subject	Evaluation of need for a REMS
Established Name	Lixisenatide
(Proposed) Trade Name	Adlyxin
Applicant	Sanofi-Aventis US LLC
Therapeutic Class	Antidiabetic drug, glucagon-like peptide 1 receptor agonist
Formulation(s)	50 mcg/mL in 3 mL prefilled pen (for 14 pre-set doses; 10 mcg per dose) and 100 mcg/mL in 3 mL prefilled pen (for 14 pre-set doses; 20 mcg per dose) for subcutaneous injection.
Dosing Regimen	Administer once daily within one hour before the first meal of the day. Initiate at 10 mcg once daily for 14 days. On day 15, increase dosage to 20 mcg once daily.
Proposed Indication(s)	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

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

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) lixisenatide is necessary to ensure the benefits of this product outweigh its risks. Sanofi-Aventis submitted a New Drug Application (NDA 208471) for lixisenatide with the proposed indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Lixisenatide is a selective dipeptidyl peptidase-4 (DPP-4)-resistant glucagon-like peptide 1 receptor agonist (GLP-1 RA). The risks associated with the use of lixisenatide are pancreatitis, hypoglycemia (with concomitant use of sulfonylurea or basal insulin), renal impairment, hypersensitivity reactions, and immunogenicity. The applicant's proposed REMS consists of a communication plan (CP) and a timetable for submission of assessments to mitigate the risk of pancreatitis.

Other drugs in the GLP-1 RA class approved by FDA required a REMS to mitigate the risks of thyroid C-cell tumor and/or pancreatitis. Exenatide (Byetta), an FDA-approved GLP-1 RA, is structurally similar to lixisenatide. Byetta had a communication plan REMS to mitigate the risk of pancreatitis and renal failure but the REMS was eliminated upon completion of all communication activities. Other FDA-approved products in the GLP-1 RA class (i.e., exenatide ER, liraglutide, albiglutide, and dulaglutide) have communication plan REMS to mitigate the risk of thyroid C-cell tumor but also communicate the risk of pancreatitis associated with these products; however, the basis for these REMS is the risk of thyroid C-cell tumor and not the risk of pancreatitis. The REMS for exenatide ER (Bydureon) was also eliminated upon completion of all communication activities. In addition, there are no postmarketing safety signals for GLP-1 RA products suggesting an increase in the reporting of pancreatitis beyond what is expected.

DRISK and the Division of Metabolism and Endocrinology Products agree that a REMS is not needed to ensure the benefits of lixisenatide outweigh its risks. The clinical data included in this application do not show a risk for thyroid C-cell tumor and the risk of pancreatitis identified with exposure to lixisenatide is consistent with that observed with other GLP-1 RAs. Available REMS assessment data for exenatide, exenatide ER, liraglutide, albiglutide and dulaglutide show that prescribers are knowledgeable about the risk of pancreatitis associated with these GLP-1 RAs suggesting that this risk message has been effectively communicated to relevant prescriber groups. In addition, there are no postmarketing safety signals for GLP-1 RA products suggesting an increase in the reporting of pancreatitis beyond what is expected. Similarly to other GLP-1 RAs, the risk of pancreatitis associated with lixisenatide does not require a boxed warning and will be communicated in the Warnings and Precautions section of the lixisenatide label. DRISK recommends maximizing labeling (e.g., box warning) before a REMS is considered.

1 Introduction

Sanofi-Aventis submitted a New Drug Application (NDA 20847) for lixisenatide with the proposed indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. This application is under review in the Division of Metabolism and Endocrinology Products (DMEP). The applicant's proposed REMS consists of a communication plan (CP) and a timetable for submission of assessments to address the risk of pancreatitis.

2 Background

2.1 PRODUCT INFORMATION

Lixisenatide, a new molecular entity, is a glucagon-like peptide 1 receptor agonist (GLP-1 RA), proposed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Glucagon-like peptide 1 (GLP-1), an incretin hormone secreted from cells in the gastrointestinal tract after ingestion of a meal, has three main effects on glucose metabolism: (1) stimulation of insulin release from the pancreatic islets through a glucose-dependent activation of the GLP-1 receptor, (2) suppression of glucagon release, and (3) delay in gastric emptying mediated through post-prandial GLP-1 receptor activation. These effects on glucose metabolism result in lowering of fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) and weight loss.

Lixisenatide is supplied as a solution for subcutaneous injection to be taken once daily within one hour prior to the first meal of the day. Lixisenatide is available as 50 mcg/mL in 3 mL prefilled pen (for 14 pre-set doses; 10 mcg per dose as an initiation dose) and 100 mcg/mL in 3 mL prefilled pen (for 14 pre-set doses; 20 mcg per dose as a maintenance dose).

FDA approved GLP-1 agonists include: exenatide, exenatide ER, liraglutide, albiglutide, and dulaglutide. Table 1 provides a comparison between all FDA-approved GLP-1 agonists. Lixisenatide is structurally similar to exenatide. Lixisenatide has a mean terminal half-life of 1.5 to 4.5 hours and preserves the delay in gastric emptying effect with chronic dosing. Other GLP-1 receptor agonists (e.g., liraglutide) have a decrease in the gastric emptying delay effect with chronic dosing probably due to tachyphylaxis.¹

Lixisenatide was first licensed in Mexico (January 2013) and the European Union (February 2013 as Lyxumia) and is currently approved in over 50 countries. The Applicant withdrew the original application for lixisenatide (NDA 204961) submitted to the FDA in 2012 pending completion of a cardiovascular outcomes trial (EFC11319 (ELIXA)). [REDACTED] (b) (4)

[REDACTED]

FDA is currently [REDACTED] (b) (4).

¹ Sanofi-Aventis, Clinical Overview for Lixisenatide, dated July 11, 2015.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 208471 relevant to this review:

- 06/08/2001: Initial IND for compound ZS42-0010 was submitted to FDA by Zealand Pharmaceuticals.
- 08/24/2004: IND sponsorship transferred to Aventis Pharmaceuticals (will later become part of the Sanofi companies); the compound was then changed from ZS42-0010 to AVE0010 Injection.
- 12/19/2007: Applicant and the FDA held an End-of-Phase 2 meeting to confirm the adequacy of the proposed development program to support the submission of the proposed new drug application (NDA).
- 11/06/2008: FDA informs Sanofi that the development of AVE0010 needed to meet new cardiovascular (CV) safety requirements.
- 04/07/2011: Sanofi submitted the protocol for the CV safety Study EFC11319 (ELIXA) and a proposal for the submission of results of the interim analyses.
- 09/20/2011: FDA provided written responses and stated that the Applicant may choose to submit the interim CV analyses with the original NDA submission by using a firewalled group within Sanofi to maintain integrity of the study.
- 11/28/2012: Type B pre-NDA meeting. The sponsor proposed voluntary risk mitigation activities instead of a REMS. FDA requested inclusion of a REMS in the NDA submission.
- 12/20/2012: NDA 204961 for lixisenatide received by FDA, including a proposed REMS for the risk of pancreatitis. The NDA was classified as 'Standard' and FDA informed the sponsor that an Advisory Committee meeting was required to discuss the application.
- 05/20/2013: Post mid-cycle teleconference with the Applicant. FDA informs Sanofi of the possibility of having a portion of the Advisory Committee meeting closed to the public in order to protect the integrity of the blinded ELIXA interim cardiovascular data.
- 08/21/2013: DRISK review entered in DARRTS. DRISK recommended the implementation of a CP REMS to address the potential risk of pancreatitis associated to other drugs in the GLP-1 RA class because of the serious, potentially life-threatening nature of pancreatitis, the large T2DM mellitus patient population potentially exposed to lixisenatide, the wide range of potential prescribers' experience in the management of T2DM, and the fact that there are other alternatives for the treatment of T2DM.
- 09/10/2013: Sanofi withdrew the NDA for lixisenatide. Sanofi determined that the evaluation of application should be based on the complete results of the ELIXA study rather than interim data. Sanofi also expressed their concern that public disclosure of early interim data could compromise the integrity of the ongoing ELIXA study.
- 10/15/2013: Type A to obtain FDA's feedback on major application deficiencies and other review-related issues.
- 06/08/2015: Type B meeting to discuss questions related to the cardiovascular outcomes trial, EFC11319 (ELIXA), timing for submission of stability data within 30 days of the NDA submission, and the REMS requirements for new GLP-1 receptor agonists. FDA encourages Sanofi to submit a REMS as part of the NDA.

- 07/27/2015: FDA receives NDA 208471 for lixisenatide, including a REMS similar to those approved for other GLP-1 RAs. The plan included a communication plan and a timetable for submission of REMS assessments.
- 01/05/2016: Mid-cycle meeting.
- 01/21/2016: Mid-cycle communication. FDA informs the sponsor that it has made a preliminary determination that a REMS will not be necessary to ensure that the benefits of the lixisenatide outweigh the risks of pancreatitis but that a final determination will be made upon completion of our review. In addition, FDA informs the sponsor that anaphylaxis and hypersensitivity reactions remain safety issues under consideration.
- 02/17/2016: Proposed proprietary name (b) (4), conditionally approved by FDA.
- 05/24/2016: Advisory Committee meeting. The advisory panel recommended approval of lixisenatide.
- 06/09/2016: The applicant withdrew the name (b) (4) and re-submitted the proposed name Adlyxin for evaluation.
- 06/14/2016: FDA grants conditional approval to the proprietary name Adlyxin
- 06/23/2016: FDA grants approval to the proprietary name Adlyxin.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Diabetes is a group of diseases (e.g., Type I diabetes, Type II diabetes, gestational diabetes, maturity-onset diabetes of youth or latent autoimmune diabetes in adults) characterized by high levels of blood glucose due problems with the production and/or function of insulin.² According to the Centers of Disease Control and Prevention (CDC), diabetes affects over 29 million Americans (9.3 % of the US population). In 2012, there were 1.7 million new cases of diagnosed diabetes among people aged 20 years or older in the US.² Diabetes may decrease life expectancy by 10-15 years and is the 7th leading cause of death in the US.² Complications of diabetes include vision loss, kidney injury, lower extremity amputation, heart attacks, and strokes. In addition, people with poorly controlled diabetes may experience decreased sense of well-being, impaired quality of life, cognitive impairment, depression, and periodontal disease among many other adverse effects.² The estimated cost of diabetes in the US (2012 data) is over \$245 billion.²

Type 2 diabetes often begins with insulin resistance and as the need for insulin rises, pancreatic beta cells gradually lose the ability to produce sufficient quantities of the hormone.³ However, the role of insulin resistance versus beta cell dysfunction differs among individuals. Glucose control tends to be more challenging over time.³ Risk factors for the development of Type 2 diabetes include older age,

² Centers for Disease Control and Prevention (CDC). National diabetes statistics report: Estimates of diabetes and its burden in the United States, 2014. Atlanta, GA: U.S. Department of Health and Human Services; 2014.

³ Patient-centered Outcomes Research Institute (PCORI), Second- and Third-Line Approaches for Type 2 Diabetes Workgroup: Topic Brief, March 7, 2016, accessed on March 10, 2016 at: <http://www.pcori.org/sites/default/files/PCORI-Type-2-Diabetes-Stakeholder-Workshop-Topic-Brief-030716.pdf>

obesity, family history of diabetes, history of gestational diabetes, impaired glucose metabolism, physical inactivity, and race/ethnicity.³

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The treatment of type 2 diabetes usually begins with lifestyle modifications (e.g., exercise, balanced nutrition, weight management) and treatment with metformin. When adequate control is not achieved with these measures other therapies are prescribed. Addition of a second line therapy is required for about 34% of recently diagnosed patients within 6 months after the diagnosis and in about 45% of the patients within 6 months after the diagnosis.⁴ Other types of drugs used in the treatment of type 2 diabetes include drugs in the following classes: sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose co-transporter 2 (SGLT-2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and insulin. However, none of these agents have demonstrated long-term efficacy and safety for all patients; therefore, there is a medical need for the development of safe and effective antihyperglycemic therapies formulated in ways that may increase compliance with therapy.

In a 2016 consensus statement on the management of type 2 diabetes, recommendations by the American Association of Clinical Endocrinologists and the American College of Endocrinology suggest that GLP-1 receptor agonists are at the top of the list of second-line treatment of type 2 diabetes.⁵ GLP-1 receptor agonists currently approved in the US include exenatide (twice-daily injection), liraglutide (once-daily injection), exenatide extended release (once-weekly injection), albiglutide (once-weekly injection), dulaglutide and (once-weekly injection).

Exenatide (Byetta) had a communication plan REMS to mitigate the risk of pancreatitis and renal failure but the REMS was eliminated upon completion of all communication activities. Other FDA-approved products in the GLP-1 RA class (i.e., exenatide ER, liraglutide, albiglutide, and dulaglutide) have communication plan REMS to mitigate the risk of thyroid C-cell tumor but also communicate the risk of pancreatitis associated with these products; however, the basis for these REMS is the risk of thyroid C-cell tumor and not the risk of pancreatitis. The REMS for exenatide ER (Bydureon) was eliminated upon completion of all communication activities.

See Table 1 in the Appendix for a comparison between all FDA-approved GLP-1 agonists.

⁴ Raebel MA, Ellis JL, Schroeder EB, et al. Intensification of antihyperglycemic therapy among patients with incident diabetes: a Surveillance Prevention and Management of Diabetes Mellitus (SUPREME-DM) study. *Pharmacoepidemiology and Drug Safety*. 2014; 23(7):699-710.

⁵ Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm – 2016 executive summary. *Endocrine Practice*. 2016;22(1):84-113.

4 Benefit Assessment

The clinical development program for lixisenatide evaluated its efficacy in achieving glycemic control in patients with type 2 diabetes mellitus. The program consisted of 22 Phase 1 studies, 5 Phase 2 and 15 Phase 3 studies evaluating the efficacy of lixisenatide as monotherapy or in combination with other approved antidiabetic treatments.¹

Following are highlights of Phase 3 studies:

- Placebo control: 9 double-blind, placebo-controlled studies (EFC6014, EFC6015, EFC6016, EFC6017, EFC6018, EFC10743, EFC10781, EFC10887, and EFC11321). The primary objective of these studies was to demonstrate the superiority of lixisenatide over placebo. Primary endpoint was change in HbA1c.^{1, 6, 7}
- Active controls:
 - 2 active-controlled studies (EFC6019 and EFC12626) in which the primary endpoint was change in HbA1c. The primary objective of these studies was to demonstrate non-inferiority of lixisenatide QD versus exenatide BID (EFC6019) and versus insulin glulisine QD and three times daily (TID) (EFC12626).¹
 - 1 active-controlled study (sitagliptin, EFC10780) in which the primary endpoint was a composite of responders for HbA1c and reduction in body weight in a specific population (obese, T2DM, younger than 50 years).¹
- Mealtime administration: 1 mealtime study (EFC12261) which compared the administration of lixisenatide before the main meal of the day and before breakfast. Primary endpoint was change in HbA1c.¹
- Cardiovascular outcome study: this study EFC11319 (ELIXA) was a double-blind, placebo-controlled CV outcome study in patients who received either lixisenatide or placebo in combination with standard-of-care treatment. Measures of glycemic control included changes in HbA1c, FPG, and body weight and did not represent main endpoints.¹
- Uncontrolled study: 1 monotherapy, safety study (LTS10888) in Japanese patients.¹

Usually, the study design included the following periods: run-in, dose initiation, treatment maintenance (with a 24-week main treatment period in most studies), and a 3-day safety follow-up.¹ Initial studies used a 2-step dose increase regimen (10 µg QD for 1 week, then 15 µg QD for 1 week, then the maintenance dose of 20 µg QD); and 3 Phase 3 studies included an arm using a 1-step dose increase (10 µg QD for 2 weeks, then the maintenance dose of 20 µg QD). Four later studies employed only the 1-step dose increase.¹

The clinical development program for lixisenatide demonstrated that it is effective in achieving and maintaining glycemic control at a maintenance dose of 20 µg QD. In placebo-controlled trials, the mean change in HbA1c from baseline to Week 12 or Week 24 in the lixisenatide treatment groups ranged from -0.71% to -0.92%.¹ Differences between lixisenatide versus placebo ranged from -0.32% to -0.88%.¹ In active-controlled trials, lixisenatide 20 µg QD achieved and maintained clinically relevant reductions in HbA1c.¹ In EFC6019, the change from baseline in HbA1c at Week 24 was -0.79% in the lixisenatide group

⁶ Lixisenatide mid-cycle meeting clinical reviewer's handout, January 5, 2016.

⁷ Suchitra Balakrishnan, MD, PhD. DMEP, Clinical Review for Lixisenatide (NDA 208471), dated July 1, 2016.

and -0.96% in the exenatide group (difference: 0.17%, 95% CI: 0.033 to 0.297%); the upper bound of the 95% CI for non-inferiority was set at 0.4%.¹ In EFC12626, lixisenatide 20 µg QD was non-inferior to insulin glulisine; the change in HbA1c from baseline to Week 26 was -0.63% in the lixisenatide group, -0.58% in the insulin glulisine QD group, and -0.84% in the insulin glulisine TID group (differences: -0.05%, 95% CI: -0.170% to 0.064%; and 0.21%, 95% CI: 0.095% to 0.328%, respectively; the upper bound of the 95% CI for non-inferiority was set at 0.4%. In EFC10780, the change in HbA1c from baseline to Week 24 was similar between the lixisenatide and sitagliptin groups (-0.66% lixisenatide; -0.72% sitagliptin).¹

5 Risk Assessment & Safe Use Conditions

Adverse events of special interest for the GLP-1 RA class include thyroid C-cell cancer and pancreatitis. See table 1 in Appendix.

Thyroid Tumors. There was an imbalance in the “Malignant or Unspecified tumor” (SMQ, MedDRA 17.1) driven by imbalances in the number of prostate cancer, colorectal cancer, and unspecified thyroid neoplasms. However, individual case assessments did not indicate a safety signal for these tumor types. In the Phase 2/3 placebo-controlled studies, the exposure-adjusted incidence rate of malignant or unspecified tumors per 100 patient-years was 1.47 with lixisenatide and 1.34 with placebo. For malignant or unspecified thyroid tumors the exposure-adjusted incidence rate per 100 patient-years was 0.22 with lixisenatide and 0.15 with placebo. Most “unspecified tumors” were associated with thyroid nodules and were non-serious. There was 1 lixisenatide patient and 2 placebo patients with confirmed thyroid cancer (exposure-adjusted incidence rate per 100 patient-years of 0.01 and 0.02, respectively).

Pancreatitis. There was no safety signal indicating an increased risk for pancreatitis in lixisenatide-treated patients. The number of patients with treatment-emergent adverse events of any type of pancreatitis was smaller in the lixisenatide group (5 patients) compared with placebo (8 patients). The exposure-adjusted incidence rate of these events per 100 patient-years was 0.09 with lixisenatide and 0.13 with placebo. The exposure-adjusted incidence rate of acute or acute on chronic pancreatitis per 100 patient-years was 0.05 with lixisenatide and 0.12 with placebo.

Allergic Reactions. The clinical development program for lixisenatide demonstrated an association between lixisenatide and hypersensitivity reactions. In Phase 2/3 trials, treatment-emergent adverse events adjudicated as allergic reactions were more common with lixisenatide (1.3%) than placebo (0.9%). The exposure-adjusted incidence rate per 100 patient years was 0.95 with lixisenatide and 0.59 with placebo. Allergic reactions adjudicated as related to lixisenatide occurred with a higher incidence for lixisenatide (0.4%; exposure-adjusted incidence rate 0.28/100 patient years) than placebo (0.2%; exposure-adjusted incidence rate 0.12/100 patient years). In addition, safety analyses showed an association between lixisenatide and systemic hypersensitivity reactions; 10 patients treated with lixisenatide reported treatment-emergent adverse events adjudicated as anaphylactic reaction or anaphylactic shock (1 patient), possibly related to lixisenatide, versus none on placebo.

The Division of Pulmonary, Allergy, and Rheumatology (DPARP) was consulted by DMEP regarding lixisenatide and severe hypersensitivity reactions that reported in the clinical development program.⁸

⁸ Stacy Chin, M.D. DPARP. Anaphylaxis in the lixisenatide clinical development program, dated April 5, 2016.

DPARP's review stated that: (1) it appears that hypersensitivity reactions, including anaphylaxis, are a shared side effect of the GLP-1 RA drug class; (2) due to differences in the identification of allergic reactions in the various GLP-1 RAs clinical programs, a direct comparison of anaphylaxis or other severe hypersensitivity reactions cannot be made between lixisenatide and other marketed drugs in this class; (3) the immunogenicity of lixisenatide (as measured by anti-drug antibody (ADA) formation) is higher (~70%) than that observed for other marketed GLP-1 RAs; and (4) the clinical relevance of ADA to lixisenatide with regard to hypersensitivity reactions and anaphylaxis is unclear.

Cardiovascular Adverse Events. The clinical development program for lixisenatide demonstrated that there was no excess risk of cardiovascular events in patients treated with lixisenatide. The cardiovascular safety profile of lixisenatide was found to be similar to that of placebo. Based on the cardiovascular outcomes trial, study EFC11319 (ELIXA), the primary composite endpoint was major adverse cardiac event (MACE) + time to first occurrence of CV death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina. The percentage of patients with a primary cardiovascular endpoint event (13.4% with lixisenatide and 13.2% with placebo) and the incidence rate per 100 patient-years (6.39 lixisenatide and 6.31 placebo) were comparable between treatment groups with a Hazards Ratio of 1.017 (95% CI, 0.886 to 1.168).

6 Analysis of Expected Postmarket Use

Lixisenatide is expected to be prescribed by the same healthcare providers currently prescribing other GLP-1 RAs in the market (e.g., endocrinologist, internists, and primary care physicians). As described in Table 1 above, the relevant GLP-1 RA prescriber population seems to be knowledgeable of the risk of pancreatitis associated with this class of drugs. Lixisenatide will be administered as a subcutaneous injection by patients themselves, their caretakers or healthcare providers in all clinical settings in which patients with type 2 diabetes receive treatment.

7 Risk Management Activities Proposed by the Applicant

The Applicant submitted a REMS similar to that of other GLP-1 RAs in the market in response to FDA's request (see Section 2.2 Regulatory History) including a REMS Document, REMS Supporting Document and REMS appended materials. The goal of the proposed REMS is: To inform healthcare professionals about the potential risk of pancreatitis associated with lixisenatide. REMS elements include a communication plan and a timetable for submission of REMS assessments. Proposed communication tools include: REMS letters, REMS factsheet, and a REMS website.

8 Discussion of Need for a REMS

DRISK and the Division of Metabolism and Endocrinology Products (DMEP) agree that a REMS is not required to ensure the benefits of lixisenatide outweigh its risk for pancreatitis. The clinical data included in this application do not show an increased risk for thyroid C-cell tumor and the risk of pancreatitis identified with exposure to lixisenatide is consistent with that observed with other GLP-1 RAs. Available REMS assessment data for exenatide, exenatide ER, albiglutide and dulaglutide show that prescribers are knowledgeable about the risk of pancreatitis associated with these GLP-1 RAs suggesting

that this risk message has been effectively communicated to relevant prescriber groups. In addition, there are no postmarketing safety signals for GLP-1 RA products suggesting an increase in the reporting of pancreatitis beyond what is expected. Similarly to other GLP-1 RAs, the risk of pancreatitis associated with lixisenatide does not require a boxed warning and will be communicated in the Warnings and Precautions section of the lixisenatide label. In general DRISK recommends maximizing labeling (e.g., box warning) before a REMS is considered.

9 Conclusion & Recommendations

The available data for efficacy and safety support approval of lixisenatide as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.⁷ DRISK and DMEP agree that a REMS is not required to ensure the benefits of lixisenatide outweigh its risk of pancreatitis. Similarly to other GLP-1 RAs, the risk of pancreatitis associated with lixisenatide does not require a boxed warning and will be communicated in the Warnings and Precautions section of the lixisenatide label. DRISK recommends maximizing labeling (e.g., box warning) before a REMS is considered.

Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Materials Reviewed

The following is a list of materials informing this review:

1. Sanofi-Aventis US. Risk Evaluation and Mitigation Strategy for Lixisenatide, submitted to FDA on July 27, 2015.
2. Sanofi-Aventis US. Proposed Prescribing Information for Lixisenatide, submitted to FDA on July 27, 2015.
3. Sanofi-Aventis US. Clinical Overview for Lixisenatide, dated July, 2015.
4. Lixisenatide mid-cycle meeting clinical reviewer's handout, January 5, 2016.
5. Julia Ju, Pharm.D., Ph.D., Social Science Reviewer, DRISK, Bydureon 2-year REMS Assessment Report review, dated May 23, 2014.
6. Julia Ju, Pharm.D., Ph.D. Victoza 6-year REMS Assessment Report review, dated June 6, 2016.
7. Debra Ryan, Pharm.D, MBA. Division of Pharmacovigilance I (DPV-I). Pharmacovigilance Memorandum for Victoza™ (liraglutide), NDA: 22-341, March 29, 2016.
8. Debra Ryan, Pharm.D, MBA, Safety Evaluator, Division of Pharmacovigilance I (DPV-I), Pharmacovigilance memorandum, dated February 29, 2016.
9. Brian Gordon, M.A., Social Science Reviewer, DRISK, Byetta 18-months REMS Assessment Report, dated June 24, 2011.
10. Amarilys Vega, MD, MPH. DRISK. REMS Review for Lixisenatide (NDA 204961), dated August 21, 2013.
11. Suchitra Balakrishnan, MD, PhD. DMEP, Clinical Review for Lixisenatide (NDA 208471), dated July 1, 2016.
12. Stacy Chin, M.D. DPARP. Anaphylaxis in the lixisenatide clinical development program, dated April 5, 2016.

APPENDIX

APPEARS THIS WAY ON ORIGINAL

Table 1. Comparison Between all FDA-approved GLP-1 Agonists

Proprietary Generic	Byetta <i>Exenatide</i>	Bydureon <i>Exenatide (ER)</i>	Victoza <i>Liraglutide</i>	Saxenda <i>Liraglutide</i>	Tanzeum <i>Albiglutide</i>	Trulicity <i>Dulaglutide</i>
Approval NDA/BLA # Sponsor	April 28, 2005 NDA 021773 Astrazeneca AB	January 27, 2012 NDA 022200 Astrazeneca AB	January 25, 2010 NDA 22341 Novo Nordisk INC	December 23, 2014 NDA 206321 Novo Nordisk INC	April 15, 2014 BLA 125431 GlaxoSmithKline LLC	September 18, 2014 BLA 125469 Eli Lilly & CO
Indication	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.	Adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of <ul style="list-style-type: none"> • 30 kg/m² or greater, or • 27 kg/m² or greater in the presence of at least one weight-related comorbid condition. 	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Frequency of Administration	Twice a day	Once weekly	Once daily	Once daily	Once weekly	Once weekly
Box Warning Risk	No	Yes Thyroid C-cell tumor	Yes Thyroid C-cell tumor	Yes Thyroid C-cell tumor	Yes Thyroid C-cell tumor	Yes Thyroid C-cell tumor
W & P	<ul style="list-style-type: none"> • Acute pancreatitis • Hypoglycemia • Renal impairment • Hypersensitivity • Gastrointestinal disease • Immunogenicity 	<ul style="list-style-type: none"> • Thyroid C-cell tumor • Pancreatitis • Hypoglycemia • Renal impairment • Hypersensitivity • Gastrointestinal disease • Injection site reactions 	<ul style="list-style-type: none"> • Thyroid C-cell tumor • Pancreatitis • Hypoglycemia • Renal impairment • Hypersensitivity 	<ul style="list-style-type: none"> • Thyroid C-cell tumor • Pancreatitis • Hypoglycemia • Renal impairment • Hypersensitivity • Heart rate increase • Acute bladder disease • Suicidal behavior/ideation 	<ul style="list-style-type: none"> • Thyroid C-cell tumor • Pancreatitis • Hypoglycemia • Renal impairment • Hypersensitivity 	<ul style="list-style-type: none"> • Thyroid C-cell tumor • Pancreatitis • Hypoglycemia • Renal impairment • Hypersensitivity • Gastrointestinal disease
REMS Milestones Approval Recent Mod Elimination	October 30, 2009 --- August 5, 2011	January 27, 2012 --- April 29, 2015	January 25, 2010 July, 2015 Active	December 23, 2014 --- Active	April 15, 2014 July, 2015 Active	September 18, 2014 July, 2015 Active
REMS Risks	<ul style="list-style-type: none"> • Pancreatitis • Renal failure 	<ul style="list-style-type: none"> • Thyroid C-cell tumor • Pancreatitis 	<ul style="list-style-type: none"> • Thyroid C-cell tumor • Pancreatitis 	<ul style="list-style-type: none"> • Thyroid C-cell tumor • Pancreatitis 	<ul style="list-style-type: none"> • Thyroid C-cell tumor • Pancreatitis 	<ul style="list-style-type: none"> • Thyroid C-cell tumor • Pancreatitis

Table 1. Comparison Between all FDA-approved GLP-1 Agonists

Proprietary Generic	Byetta <i>Exenatide</i>	Bydureon <i>Exenatide (ER)</i>	Victoza <i>Liraglutide</i>	Saxenda <i>Liraglutide</i>	Tanzeum <i>Albiglutide</i>	Trulicity <i>Dulaglutide</i>
Risk Data Sources	<ul style="list-style-type: none"> Thyroid C-cell tumor: N/A Pancreatitis labeling based on Byetta’s postmarketing case reports.⁹ 	<ul style="list-style-type: none"> Thyroid C-cell tumor: Labeling based on nonclinical data and liraglutide medullary thyroid carcinoma (MTC) postmarketing case reports.¹⁰ Pancreatitis: Labeling based on postmarketing case reports for Byetta and Bydureon. Error! Bookmark not defined. 	<ul style="list-style-type: none"> Thyroid C-cell tumor labeling based on nonclinical data and liraglutide MTC postmarketing case reports.¹¹ Pancreatitis: 2.7 cases per 1000 patient-years in clinical trials. Signal supported by postmarketing case reports for liraglutide.¹¹ 	<ul style="list-style-type: none"> Thyroid C-cell tumor labeling based on nonclinical data and liraglutide MTC postmarketing case reports.¹² Pancreatitis: 0.3% in Saxenda-treated patients in clinical trials. Signal supported by postmarketing case reports for liraglutide.¹² 	<ul style="list-style-type: none"> Thyroid C-cell tumor labeling based on nonclinical data and liraglutide MTC postmarketing case reports.¹³ Pancreatitis: 0.3% in Tanzeum-treated patients in clinical trials.¹³ 	<ul style="list-style-type: none"> Thyroid C-cell tumor labeling based on nonclinical data and liraglutide MTC postmarketing case reports.¹⁴ Pancreatitis: 1.4 cases per 1000 Trulicity-treated patient-years in clinical trials.¹⁴
REMS Elements	Medication Guide Communication Plan Timetable	Communication Plan Timetable	Communication Plan Timetable	Communication Plan Timetable	Communication Plan Timetable	Communication Plan Timetable
REMS Assessment (most recent)	<ul style="list-style-type: none"> Thyroid C-cell tumor: N/A Pancreatitis: Prescribers’ knowledge of pancreatitis-related REMS messages ranged between 93-99%. Time to 90% discontinuation decreased from 21 days to seven days.¹⁵ 	<ul style="list-style-type: none"> Thyroid C-cell tumor: Prescribers’ knowledge of thyroid C-cell tumors -related REMS messages was 74%.¹⁶ Pancreatitis: Prescribers’ knowledge of pancreatitis-related REMS messages was 90%. REMS elimination: 	<ul style="list-style-type: none"> Thyroid C-cell tumor: Prescriber’s knowledge of thyroid C-cell tumors -related REMS messages ranged from 83-85% respectively.^{17,18} Percentage of prescribers answering correctly at least 3 out of 4 questions related to the risk of MTC ranged from 81-83%.^{17,18} Pancreatitis: Prescriber’s knowledge of pancreatitis thyroid C-cell tumors -related 	<ul style="list-style-type: none"> Thyroid C-cell tumor: <i>Pending REMS Assessment Report review.</i> Pancreatitis: <i>Pending REMS Assessment Report review.</i> 	<ul style="list-style-type: none"> Thyroid C-cell tumor: 80% responded to 75% of the questions correctly.¹⁹ Pancreatitis: 87% of respondents answered at least 75% of questions about the risk of pancreatitis correctly.¹⁹ 	<ul style="list-style-type: none"> Thyroid C-cell tumor: 86% of prescribers were aware of the potential risk of MTC.²⁰ Pancreatitis: 95% of prescribers were aware of the risk of pancreatitis with

⁹ Byetta product labeling accessed March 17, 2016 at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=53d03c03-ebf7-418d-88a8-533eabd2ee4f>.

¹⁰ Bydureon product labeling accessed March 17, 2016 at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=71fe88be-b4e6-4c2d-9cc3-8b1864467776>.

¹¹ Victoza prescribing information accessed March 17, 2016 at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=5a9ef4ea-c76a-4d34-a604-27c5b505f5a4>.

¹² Saxenda product labeling accessed on March 17, 2016 at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3946d389-0926-4f77-a708-0acb8153b143>.

¹³ Tanzeum product labeling accessed March 17, 2016 at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=5fcad939-76e7-49cf-af94-4e6aef17901f>.

¹⁴ Trulicity product labeling accessed on March 17, 2016 at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=463050bd-2b1c-40f5-b3c3-0a04bb433309#section-5.2>.

¹⁵ Brian Gordon, M.A. DRISK. Byetta 18-months REMS Assessment Report, dated June 24, 2011.

¹⁶ Naomi Redd, Pharm.D. DRISK. Bydureon REMS review dated April 9, 2015.

¹⁷ Julia Ju, Pharm.D., Ph.D. DRISK. Victoza 6-year REMS Assessment Report review, dated June 6, 2016.

¹⁸ Novo Nordisk. Victoza, response to FDA Information Request dated March 14, 2016. Received by FDA on March 25, 2016.

¹⁹ Julia Ju, Pharm.D., Ph.D. DRISK. Tanzeum 18-months REMS Assessment Report review dated March 29, 2016.

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Proprietary Generic	Byetta <i>Exenatide</i>	Bydureon <i>Exenatide (ER)</i>	Victoza <i>Liraglutide</i>	Saxenda <i>Liraglutide</i>	Tanzeum <i>Albiglutide</i>	Trulicity <i>Dulaglutide</i>
	REMS elimination: CP was completed and the REMS goals were met.	CP was completed and the REMS goals were met. ¹⁶	REMS messages ranged from 83-91%. Percentage of prescribers answering correctly the 3 questions related to pancreatitis ranged from 72-81%. ^{17,18}			Trulicity. ²⁰

²⁰ Eli Lilly. REMS Assessment Report for Trulicity, received by FDA on March 8, 2016.

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/s/

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