

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208673Orig1s000

**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	208673
PDUFA Goal Date	August 21, 2016
OSE RCM #	2015-2774 2015-2777
Reviewer Name(s)	Amarilys Vega, MD, MPH
DRISK Team Leader	Naomi Redd, Pharm.D
Division Director	Cynthia LaCivita, Pharm.D
Review Completion Date	August 16, 2016
Subject	Evaluation of need for a REMS
Established Name	Lixisenatide/Insulin Glargine
Trade Name	Soliqua
Applicant	Sanofi-Aventis US LLC
Therapeutic Class	Antidiabetic drug, glucagon-like peptide 1 receptor agonist
Formulation	3 mL SoloStar® disposable prefilled pen - 100 units/mL insulin glargine and 33 mcg/mL lixisenatide
Dosing Regimen	Administer subcutaneously once a day within the hour prior to the first meal of the day (b) (4)
Proposed Indication(s)	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, when treatment with both insulin glargine and lixisenatide is appropriate.

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EXECUTIVE SUMMARY

Sanofi-Aventis submitted a New Drug Application (NDA 208673) for a fixed-ratio combination (FRC) product including lixisenatide (NDA 208471, approved by FDA on July 27, 2016) in combination with Lantus® (insulin glargine, NDA 021081) for the proposed indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both insulin glargine and lixisenatide is appropriate. This application is under review in the Division of Metabolism and Endocrinology Products (DMEP).

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, anaphylaxis/hypersensitivity reactions, and immunogenicity. Insulin glargine (NDA 021081), an insulin analogue, is approved for once-daily subcutaneous administration for the treatment of patients with type 1 diabetes mellitus or patients with type 2 diabetes mellitus, who require basal (long-acting) insulin for the control of hyperglycemia. The risks associated with the use of insulin glargine include hypoglycemia, hypersensitivity reactions, and hypokalemia. The applicant submitted a proposed risk evaluation and mitigation strategy (REMS), [REDACTED] (b) (4)

[REDACTED]. Lixisenatide was approved by FDA without a REMS.

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 met its goals and was released 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) met its goals and was also released 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 DMEP agree that a REMS is not needed to ensure the benefits of the lixisenatide/insulin glargine FRC 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 the lixisenatide/insulin glargine FRC 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 the lixisenatide/insulin glargine FRC does not require a boxed warning and will be communicated in the Warnings and Precautions section of the lixisenatide/insulin glargine FRC label.

1 Introduction

Sanofi-Aventis submitted a New Drug Application (NDA 208673) for a fixed-ratio combination (FRC) product including lixisenatide (NDA 208471, approved by FDA on July 27, 2016) in combination with Lantus® (insulin glargine, NDA 021081) for the proposed indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both insulin glargine and lixisenatide is appropriate.

This application is under review in the Division of Metabolism and Endocrinology Products (DMEP). The applicant submitted a proposed REMS, [REDACTED] (b) (4) [REDACTED]. Lixisenatide was approved by the FDA without a REMS.

2 Background

2.1 PRODUCT INFORMATION

Lixisenatide. 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. FDA approved GLP-1 agonists include: exenatide, exenatide extended-release (ER), liraglutide, albiglutide, and dulaglutide. Lixisenatide is structurally similar to exenatide. 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)). Lixisenatide was approved by FDA in July 2016 without a REMS.

Insulin glargine. Insulin glargine (NDA 021081), an insulin analogue, is approved for once-daily subcutaneous administration for the treatment of patients with type 1 diabetes mellitus or patients with type 2 diabetes mellitus, who require basal (long-acting) insulin for the control of hyperglycemia.

Combination product insulin glargine/lixisenatide. The rationale for this FRC is that insulin glargine and lixisenatide complement each other given that insulin glargine targets fasting glucose levels and lixisenatide has an effect on postprandial plasma glucose levels. Combining these two products into one dosage form can reduce daily injection burden. The lixisenatide/insulin glargine FRC product is available as solution for injection containing 100 U/mL insulin glargine and 50 or 33 µg/mL lixisenatide.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 208673 relevant to this review:

- 04/20/2000: NDA 021081 for insulin glargine recombinant (Lantus) was approved by FDA.
- 12/20/2012: NDA 204961 for lixisenatide received by FDA, including a proposed REMS for the risk of pancreatitis.

- 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.
- 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.
- 12/21/2015: FDA receives NDA 208673 for the FRC for lixisenatide and insulin glargine.
- 01/21/2016: Mid-cycle communication for NDA 204961 for lixisenatide. FDA informed 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 FDA's review.
- 04/01/2016: FDA completed its review of the proposed proprietary names, Soliqua (b) (4) and Soliqua (b) (4) and concluded that the name, Soliqua, and the modifier, (b) (4) are acceptable but the proposed name modifiers, (b) (4) are unacceptable because they may cause medication errors.
- 04/05/2016: Mid-cycle communication letter. The letter communicated to the sponsor that a REMS was not necessary for communicating the risk of pancreatitis. In addition, the Agency communicated concerns about the risk of anaphylaxis with lixisenatide, the interpretability of efficacy data, limitations of insulin dosing, and potential risk of medication errors.
- 05/24/2016: Advisory Committee meeting. The advisory panel recommended approval, the vote was 12:2 in favor of the approval of lixisenatide and lixisenatide/insulin glargine FRC. However, panel members expressed concern about potential medication errors with the lixisenatide/insulin glargine FRC injection device (e.g., color of injection pens, dosing "unit").
- 06/16/2016: The sponsor submitted a request for evaluation of the following options for proprietary name: SOLIQUA™ and (b) (4) or SOLIQUA™ and (b) (4). The evaluation of these proprietary names is still ongoing.
- 07/27/2016: Lixisenatide (NDA 208471) approved by FDA. 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.¹ 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.¹ Diabetes may decrease life expectancy by 10-15 years and is the 7th leading cause of death in the US.¹ 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.¹ The estimated cost of diabetes in the US (2012 data) is over \$245 billion.¹

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.² However, the role of insulin resistance versus beta cell dysfunction differs among individuals. Glucose control tends to be more challenging over time.² Risk factors for the development of Type 2 diabetes include older age, obesity, family history of diabetes, history of gestational diabetes, impaired glucose metabolism, physical inactivity, and race/ethnicity.²

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The treatment of type 2 diabetes usually begins with lifestyle modifications (e.g., exercise, balanced nutrition, weigh 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.³ 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.

¹ 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.

² 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>

³ 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.

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.⁴ 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 (once-weekly injection), and lixisenatide (once-daily injection).

Exenatide (Byetta) had a communication plan REMS to mitigate the risk of pancreatitis and renal failure but the REMS met its goals and 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) met its goals and was eliminated upon completion of all communication activities.

4 Benefit Assessment

The clinical development program for lixisenatide/insulin (b) (4) evaluated the efficacy of the FRC in achieving glycemic control in a wide range of patients with type 2 diabetes mellitus, including patients with suboptimal control on one or more oral antidiabetic agents or uncontrolled on basal insulin \pm 1 to 2 oral antidiabetic agents. The completed clinical development program for the lixisenatide/insulin glargine FRC included 2,229 randomized patients included in six Phase 1 trials, one Phase 2 proof-of-concept study, and two Phase 3 pivotal confirmatory trials.

Following are highlights of Phase 3 studies.

EFC12404 (Phase 3): A randomized, 30 week, active-controlled, open label, 3-treatment arm (FRC, insulin glargine (100 U/mL) alone, lixisenatide alone), parallel group multicenter study comparing the efficacy and safety of lixisenatide/insulin glargine FRC to insulin glargine (100 U/mL) alone and to lixisenatide alone, all treatments on top of metformin in patients with type 2 diabetes mellitus. Randomization was 2:2:1 (FRC (469): insulin glargine (467): lixisenatide (234)).

Co-primary endpoints and study findings:

- (1) Superiority of the lixisenatide/insulin glargine FRC versus lixisenatide – LS mean HbA1c difference FRC vs. lixisenatide -0.78 (95% CI, -0.898 to -0.665).
- (2) Non-inferiority of the lixisenatide/insulin glargine FRC vs. insulin glargine in change in HbA1c from baseline to Week 30 – LS mean HbA1c difference FRC vs. insulin glargine -0.29 (95% CI, 0.384 to -0.194).

EFC12405 (Phase 3): A randomized, 30-week, treat-to-target, active controlled, open-label, 2-treatment arm (FRC, insulin glargine (100 U/mL) alone), parallel group, multinational study comparing the efficacy

⁴ 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.

and safety of lixisenatide/insulin glargine FRC to insulin glargine alone (100 U/mL) (both treatments with or without metformin). Randomization was 1:1 (FRC (367): Insulin glargine (100 U/mL) alone (369)). Primary endpoint was superiority of the lixisenatide/insulin glargine FRC versus insulin glargine in change in HbA1c from baseline to Week 30 (LS mean HbA1c difference vs. insulin glargine -0.52 (95% CI, -0.633 to -0.397)).

5 Risk Assessment & Safe Use Conditions

The safety database included data from the two phase 3 studies: lixisenatide (233), insulin glargine (832) and lixisenatide/insulin glargine FRC (834). Adverse events of special interest for the GLP-1 RA class include thyroid C-cell cancer and pancreatitis.

The safety profile of the lixisenatide/insulin glargine FRC is consistent with the profiles of lixisenatide and insulin glargine; generally falling in between the profiles of its individual components (e.g., SOC Gastrointestinal disorders – insulin glargine 23.8%, FRC 43.4%, lixisenatide 74.7%; SOC Infections and infestations – insulin glargine 41.1%, FRC 41.1%, lixisenatide 37.8%).⁵

Common Adverse Events. Included: nausea/vomiting (lixisenatide 26.6%, insulin glargine 3%, FRC 11%); diarrhea (lixisenatide 9%, insulin glargine 3.6%, FRC 7%) and headaches (lixisenatide 7.7%, insulin glargine 3%, FRC 5.5%).⁵

Deaths. There were 10 deaths reported in the two phase 3 studies; however, there was no predominant, single cause of death for any of the treatment arms (lixisenatide 0.4%, insulin glargine 0.7%, FRC 0.4%).⁵

Hypoglycemia. Symptomatic hypoglycemia was more frequently reported in the insulin glargine group and lixisenatide/insulin glargine FRC group (Study EFC 1204: lixisenatide 6.4% vs. insulin glargine 23.6% vs. FRC 25.6%; Study EFC 12405: insulin glargine 42.5% vs. FRC 40%).⁵

Thyroid Tumors. There was no safety signal indicating an increased risk for benign thyroid disorders in lixisenatide or lixisenatide/insulin glargine FRC treated patients in clinical trials.⁵

Pancreatitis. There was no safety signal indicating an increased risk for pancreatitis in lixisenatide or lixisenatide/insulin glargine FRC treated patients in clinical trials.⁵

Allergic Reactions. Potential lixisenatide/insulin glargine FRC risks associated with the lixisenatide component include increased immunogenicity of lixisenatide and the potential clinical risk of hypersensitivity reactions.^{5,6}

Medication Errors. There is a potential risk for medication errors because the lixisenatide/insulin glargine FRC is a multi-ingredient product with different terms of measurement and two different devices.⁶

Cardiovascular Adverse Events. The clinical development program for lixisenatide and lixisenatide/insulin glargine FRC 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.^{5,7}

⁵ EMDAC FDA Background Document, May 2016.

⁶ EMDAC FDA Slides, May 2016.

⁷ EMDAC Sanofi Slides, May 2016.

6 Analysis of Expected Postmarket Use

Lixisenatide/insulin glargine FRC 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). Based on data from REMS assessment reports, the relevant GLP-1 RA prescriber population seems to be knowledgeable of the risk of pancreatitis associated with this class of drugs. Lixisenatide/insulin glargine FRC 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 Discussion of Need for a REMS

Lixisenatide was approved by FDA in July 2016 without a REMS. At the time when this review was completed, the assessment of the overall benefits and risks of lixisenatide/insulin glargine FRC was ongoing. An advisory committee meeting was held on May 25, 2016 to discuss the lixisenatide/insulin glargine FRC benefit:risk profile. The advisory panel voted 12:2 in favor of the approval of lixisenatide/insulin glargine FRC; however, the committee expressed concerns about the need to characterize the appropriate patient population to receive treatment with this product and concerns about the distinction of the 2 proposed injection devices.⁸

DRISK and the Division of Metabolism and Endocrinology Products (DMEP) agree that a REMS is not required to ensure the benefits of lixisenatide/insulin glargine FRC outweigh its risks, including the 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/insulin glargine FRC 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/insulin glargine FRC does not require a boxed warning and will be communicated in the Warnings and Precautions section of the lixisenatide/insulin glargine FRC label.

8 Risk Management Activities Proposed by the Applicant

The Applicant submitted a REMS [REDACTED] (b) (4)

[REDACTED]

⁸ FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.

9 Conclusion & Recommendations

Based on the available data, the benefit-risk profile of the lixisenatide/insulin glargine FRC, DRISK and DMEP agree that a REMS is not required to ensure the benefits of lixisenatide/insulin glargine FRC outweigh its risk for pancreatitis. At the time of this review, evaluation of safety information and labeling was ongoing. 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. Sanofi-Aventis US. EMDAC Briefing Document and Slides, May 2016.
5. FDA EMDAC Briefing Document and Slides, May 2016.
6. Lixisenatide mid-cycle meeting clinical reviewer's handout, January 5, 2016.
7. Julia Ju, Pharm.D., Ph.D, Social Science Reviewer, DRISK, Bydureon 2-year REMS Assessment Report review, dated May 23, 2014.
8. Julia Ju, Pharm.D., Ph.D. Victoza 6-year REMS Assessment Report review, dated June 6, 2016.
9. Debra Ryan, PharmD, MBA. Division of Pharmacovigilance I (DPV-I). Pharmacovigilance Memorandum for Victoza™ (liraglutide), NDA: 22-341, March 29, 2016.
10. Debra Ryan, PharmD, MBA, Safety Evaluator, Division of Pharmacovigilance I (DPV-I), Pharmacovigilance memorandum, dated February 29, 2016.
11. Brian Gordon, M.A., Social Science Reviewer, DRISK, Byetta 18-months REMS Assessment Report, dated June 24, 2011.
12. Amarilys Vega, MD, MPH. DRISK. REMS Review for Lixisenatide (NDA 204961), dated August 21, 2013.
13. Stacy Chin, M.D. DPARP. Anaphylaxis in the lixisenatide clinical development program, dated April 5, 2016.
14. Lixisenatide approval letter, dated July 27, 2016.

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/s/

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08/16/2016

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08/16/2016
Concur