CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208583Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

REMS REVIEW

Date: November 21, 2016

Reviewer: Mei-Yean Chen, Pharm.D., Risk Management Analyst, Division of Risk Management (DRISK)

Team Leader: Naomi Redd, Pharm.D., Team Leader, DRISK
Division Director: Cynthia LaCivita, Pharm.D., DRISK

Subject: Evaluation of REMS submission from November 15, 2016 (sequence #66)

Drug Name(s): Xultophy 100/3.6 (insulin degludec and liraglutide injection)

Therapeutic class: Antidiabetic agent (ultra-long acting basal insulin analogue; glucagon like peptide 1 receptor agonist)

Dosage forms:

OND Review Division: Division of Metabolism and Endocrinology Products (DMEP)

Application Type/Number: NDA 208583

Supplement # and Date Received: Supplement 67/Sequence 66, received November 15, 2016

Applicant/sponsor: Novo Nordisk

OSE RCM #: 2015-2101 and 2015-2086
1. INTRODUCTION

This is a review of the Novo Nordisk proposed risk evaluation and mitigation strategy (REMS) amendment for Xultophy 100/3.6 (insulin degludec and liraglutide injection) (NDA 208583) received November 15, 2016. This review evaluates the amendment to the Xultophy REMS due to proprietary name change from Xultophy to Xultophy 100/3.6, and change of indication.

1.1 BACKGROUND

Novo Nordisk originally submitted a New Drug Application (NDA 208583) for Xultophy on September 14, 2015, a combination product (insulin degludec/liraglutide), as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus via a once daily subcutaneous injection. The applicant’s proposed REMS consists of a communication plan (CP) and a timetable for submission of assessments.

The proprietary name Xultophy was granted on November 12, 2015. On September 1, 2016, the FDA held a telephone conference with the applicant to discuss the need to have a proprietary name that would convey to health care practitioners the presence of two ingredients in the product to avoid potential medication errors. On September 6, 2016, the applicant submitted a request for a new proprietary name review to include the strength of insulin and liraglutide. On September 22, 2016, the Division of Medication Error Prevention and Analysis (DMEPA) granted the proprietary name of Xultophy 100/3.6. After the new proprietary name was granted, the applicant submitted the REMS amendment to include this name change in the REMS document and REMS materials. During the review of this submission, it was noted that the applicant had not included the new proprietary name on all the slides in the REMS presentation. On November 2, 2016, the applicant submitted a REMS amendment to include the name change on all of the slides in the REMS presentation, the REMS document and all of the other REMS materials. During this review, a change in the indication was also granted.

The indication was changed to:

“Xultophy 100/3.6 is a combination of insulin degludec, a long-acting human insulin analog, and liraglutide, a glucagon-like peptide (GLP-1) receptor agonist, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin (less than 50 units daily) or liraglutide (less than or equal to 1.8 mg daily)”.

On November 15, 2016, the applicant amended their proposed REMS submission including the REMS Supporting Document to align the change of indication per DMEP’s request on November 9, 2016.

1.2 REGULATORY HISTORY

- On November 12, 2015, DMEPA granted proprietary name of Xultophy
On September 1, 2016, the agency recommended through a telephone conference with the applicant to use Xultophy 100/3.6 to help to convey to health care practitioners the presence of two ingredients in the product.

On September 22, 2016, DMEPA granted proprietary name of Xultophy 100/3.6

On September 30, 2016, the applicant submitted the REMS amendment of REMS document and materials (sequence #62) to include this name change. This amendment missed one name change on one slide.

On November 2, 2016, the applicant submitted the REMS amendment of REMS document and materials to include all the name change (sequence#64)

On November 15, 2016, the applicant re-submitted the REMS amendment of REMS document and materials to reflect the change of indication (sequence # 66) which was requested by DMEP on November 9, 2016

2.0 MATERIALS REVIEWED

- Vega A, DRISK REMS Review, July 14, 2016
- Vega A, Petruccelli M, Labeling PMR/PMC Discussion Comments in DARRTS, August 17, 2016
- Vega A, Petruccelli M, Labeling PMR/PMC Discussion Comments in DARRTS, August 23, 2016
- Vega A, DRISK REMS Review, August 28, 2016
- August 30, 2016, REMS final submission, DARRTS supplement 60/sequence 59
- September 20, 2016, Conrad A, DMEPA Proprietary Name Review
- September 30, 2016, REMS/amendment, DARRTS supplement 63/sequence 62
- November 2, 2016, REMS/amendment, DARRTS supplement 65/sequence 64
- November 15, 2016, REMS/amendment, DARRTS supplement 67/sequence 66

3.0 REMS SUBMISSION

The REMS amendment submitted on November 15, 2016 (Sequence 66) includes the new proprietary name, the updated indication, the REMS materials, REMS document, and REMS Supporting Document. The sponsor did not propose any additional changes. DRISK finds the REMS acceptable and and recommends approval.
4. CONCLUSION AND RECOMMENDATIONS

DRISK agrees with all the changes proposed by the applicant in this amendment and recommends approval of the REMS.

5. APPENDICES

- REMS Document
- REMS Materials
  1. REMS Fact Sheet
  2. REMS Letter to Healthcare Provider
  3. REMS Letter to Professional Societies
  4. REMS Website
  5. REMS Slides

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/s/

MEI-YEAN T CHEN
11/21/2016

CYNTHIA L LACIVITA
11/21/2016
Concur
Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF DRUG EVALUATION II
DIVISION OF METABOLISM AND ENDOCRINOLOGY PRODUCTS

NDA/BLA #s: NDA 208583
Products: XULTOPHY 100/3.6 (insulin degludec and liraglutide injection)
APPLICANT: Novo Nordisk, Inc.
FROM: Jennifer Rodriguez Pippins, M.D., M.P.H.
DATE: November 7, 2016

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for XULTOPHY 100/3.6 (insulin degludec and liraglutide injection) to ensure that the benefits of the drug outweigh the potential risk of medullary thyroid carcinoma identified in non-clinical studies of liraglutide and other glucagon-like peptide (GLP)-1 receptor agonists, and the risk of acute pancreatitis, identified in the clinical trial data and postmarketing reports for members of the GLP-1 receptor agonist class, including liraglutide.

In reaching this determination, we considered the following:

A. Diabetes affects more than 29 million people in the United States, with Type 2 diabetes accounting for 90 to 95 percent of all diagnosed cases.¹

B. Patients with type 2 diabetes who require anti-diabetic medication for glycemic control are at risk for a variety of serious complications including blindness, kidney damage, nerve damage and atherosclerotic cardiovascular disease.

C. XULTOPHY 100/3.6 (insulin degludec and liraglutide injection) has been studied in patients converting from GLP-1 receptor agonist therapy and in patients converting from basal insulin therapy. In the trial evaluating patients converting from GLP-1 receptor agonist therapy, XULTOPHY 100/3.6 (insulin degludec and liraglutide injection) was shown to achieve a reduction in hemoglobin A1c over 26 weeks of 0.94% compared to patients treated with GLP-1 agonist. In a trial evaluating patients converting from basal insulin therapy, XULTOPHY 100/3.6 (insulin degludec and liraglutide injection) was shown to achieve a reduction in hemoglobin A1c over 26 weeks of 0.89% compared to patients treated with basal insulin. In both trials, patients were on additional background antidiabetic agents. Some of the Type 2 diabetes complications listed above can be prevented or delayed with good glycemic control. XULTOPHY 100/3.6 (insulin degludec and liraglutide injection) is an option for those individuals who are inadequately treated with lifestyle modification and are inadequately controlled on less than 50 units of basal insulin daily or a GLP-1 receptor agonist.

D. The expected duration of therapy is over a patient’s lifetime.

E. In addition to the most serious risk of medullary thyroid carcinoma and acute pancreatitis, XULTOPHY 100/3.6 (insulin degludec and liraglutide injection) also has the following risks: hypoglycemia, hypersensitivity, renal impairment, and gastrointestinal events such as nausea and diarrhea.

F. XULTOPHY 100/3.6 is a new molecular entity.

The elements of the REMS will be a communication plan and a timetable for submission of assessments of the REMS.
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/s/

JENNIFER R PIPPINS
11/21/2016
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<td>Kate Oswell, MA</td>
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<td>Division Director</td>
<td>Cynthia LaCivita, Pharm.D</td>
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1 Introduction

This review by the Division of Risk Management (DRISK) evaluates changes proposed by Novo Nordisk to the risk evaluation and mitigation strategy (REMS) for the combination product Xultophy (insulin degludec and liraglutide [rDNA origin] injection) submitted to FDA on August 25, 2016 (Seq. No. 0058). Novo Nordisk originally submitted a New Drug Application (NDA 208583) for Xultophy on September 14, 2015 (NDA 208583), a combination product, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus via a once-daily subcutaneous injection. This application is currently 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.

2 Background

DRISK review of the proposed REMS for Xultophy, dated July 14, 2016, included detailed comments to the sponsor. In response to the Agency’s comments (sent to the sponsor on July 19, 2016), Novo Nordisk submitted an amendment to the Xultophy REMS on July 29, 2016. In response to this amendment, FDA provided additional comments on August 17, 2016, which were entered in DARRTS and sent to the sponsor by Marisa Petruccelli, application project manager (COR-NDAIR-23 (Labeling PMR/PMC Discussion Comments)).

Novo Nordisk saw discrepancies between the July 19 and August 17 comments and requested clarification from FDA. DMEP and DRISK representatives held a teleconference with Novo Nordisk on August 22, 2016 to provide clarification on the comments provided by FDA. During the discussion, FDA provided written clarification points along with REMS documents in tracked changes (i.e., REMS Supporting Document, REMS Letter for Healthcare Providers, REMS Letter for Professional Societies, REMS Factsheet, REMS Slides and REMS Website). See two sets of comments (COR-NDAIR-23 (Labeling PMR/PMC Discussion Comments) entered in DARRTS on August 23, 2016 by Marisa Petruccelli.

Additional clarification was requested by Novo Nordisk on August 23, 2016 via email. DRISK provided a response (via email) on August 24, 2016 (see comments entered in DARRTS on August 24, 2016 by Marisa Petruccelli (COR-NDAIR-23 (Labeling PMR/PMC Discussion Comments).

This review evaluates the amendment to the Xultophy REMS received by FDA on August 25, 2016 (Seq. No. 0058).

3 Review of REMS Amendment

A version of the REMS Document was not included in this submission because DRISK had already agreed with the version of the REMS Document submitted by Novo Nordisk on July 29, 2016. Line numbering must be removed from the final version of the REMS Document and the date must reflect the month and year of approval.

1 FDAAA factor (F): Whether the drug is a new molecular entity.
DRISK agrees with all the changes proposed by the sponsor in this amendment. Line numbering must be removed from the final version of all the REMS materials (letters, factsheet, and REMS Supporting Document).

4 Conclusions and Recommendations

DRISK agrees with all the revisions to the REMS materials included in Novo Nordisk’s submission from August 25, 2016 and with the proposed REMS Document submitted to the Agency on July 29, 2016 (Seq. No. 0053) with the exception of the inclusion of line numbers in some of the materials. DRISK recommends approval of the Xultophy REMS contingent upon the removal of line numbers. The Agency will fill in the date of approval in final approved version of the REMS.

DRISK requests DMEP sends comments included in section 5 of this review.

5 Comments for the Applicant

Following are comments regarding the Xultophy REMS Document, REMS materials and REMS Supporting Document.

Line numbering must be removed from the final version of the REMS Document. The Agency will fill in the date of approval in final approved version of the REMS. In addition, line numbering must be removed from the final version of all the REMS materials (letters, factsheet, and REMS Supporting Document).

Submit final, clean versions of all REMS materials.
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/s/

AMARILYS VEGA
08/28/2016

CYNTHIA L LACIVITA
08/28/2016
concur
Application Type  NDA
Application Number  208583
PDUFA Goal Date  September 14, 2016
OSE RCM #  2015-2101 and 2015-2086
Reviewer Name(s)  Amarilys Vega, MD, MPH
                  Kate Oswell, MA
DRISK Team Leader  Naomi Redd, Pharm.D
Division Director  Cynthia LaCivita, Pharm.D
Review Completion Date  July 14, 2016
Subject  Evaluation of need for a REMS
Established Name  Insulin degludec/liraglutide
(Proposed) Trade Name  Xultophy
Applicant  Novo Nordisk
Therapeutic Class  Antidiabetic agent (ultralong-acting basal insulin analogue; glucagon-like peptide 1 receptor agonist)
Formulation(s)  3 mL pre-filled, multi-dose pen containing 100 units insulin degludec and 3.6 mg liraglutide per mL for subcutaneous injection
Dosing Regimen  Once daily
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This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the combination product Xultophy (insulin degludec and liraglutide [rDNA origin] injection) is necessary to ensure the benefits of this product outweigh its risks. Novo Nordisk submitted a New Drug Application (NDA 208583) for Xultophy as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus via a once-daily subcutaneous injection (b)(4). The risks associated with the use of Xultophy are thyroid C-cell tumors, pancreatitis, hypoglycemia, renal impairment, hypersensitivity and allergic reactions and fluid retention and congestive heart failure with concomitant use of a peroxisome proliferator-activated receptor (PPAR)-gamma agonists.

Insulin degludec is approved by FDA as Tresiba (NDA 203314, September 25, 2015) to improve glycemic control in adults with diabetes mellitus. Liraglutide is approved by FDA as Victoza (NDA 22341, approved January 25, 2010) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and as Saxenda (NDA 206321, approved December 23, 2014) as an 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 30 kg/m² or greater (obese), or 27 kg/m² or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia). Both Victoza and Saxenda have a boxed warning for the risk of thyroid C-cell tumor and a communication plan (CP) REMS to mitigate this risk and the risk of pancreatitis. Other FDA-approved products in the GLP1RA class (i.e., exenatide, exenatide extended release (ER), liraglutide, albiglutide, and dulaglutide) currently have, or have had at some point during the product’s lifecycle, a CP REMS to mitigate the risk of thyroid C-cell tumor and 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 applicant’s proposed REMS for Xultophy is similar to the Victoza REMS and includes a CP and a timetable for submission of assessments. Consistent with prior FDA regulatory actions for liraglutide products, DRISK and the Division of Metabolism and Endocrinology Products agree that a CP REMS is needed to ensure that the benefits of Xultophy outweigh it risk of thyroid C-cell tumor. Similarly to other GLP-1 RA CP REMS, the Xultophy REMS will also address the risk of pancreatitis.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the combination product Xultophy (insulin degludec and liraglutide [rDNA origin] injection) is necessary to ensure the benefits of this product outweigh its risks. Novo Nordisk submitted a New Drug Application (NDA 208583) for Xultophy, a combination product, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus via a once-daily subcutaneous injection (b)(4). This application is under review in the

1 FDAAA factor (F): Whether the drug is a new molecular entity.
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.

2 Background

2.1 Product Information

Xultophy is a combination of insulin degludec, a long-acting basal insulin, and liraglutide, a glucagon-like peptide-1 (GLP1) receptor agonist (GLP-1RA) administered as a single daily injection. Insulin degludec targets increased fasting glucose while liraglutide targets increased fasting glucose and prandial glucose peaks. Xultophy is dosed once daily. Xultophy is available as a 3 mL pre-filled, multi-dose pen containing 100 units insulin degludec and 3.6 mg liraglutide per mL. Similar to other antidiabetic agents, treatment with Xultophy is anticipated to be long-term (chronic use).

Insulin degludec is approved by FDA as Tresiba (NDA 203314, September 25, 2015) to improve glycemic control in adults with diabetes mellitus. Liraglutide is approved by FDA as Victoza (NDA 22341, January 25, 2010) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and as Saxenda (NDA 206321, December 23, 2014) as an 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 30 kg/m2 or greater (obese), or 27 kg/m2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia).

Both Victoza and Saxenda have a boxed warning for the risk of thyroid C-cell tumor and a communication plan (CP) REMS to mitigate this risk and the risk of pancreatitis.

Xultophy was granted marketing authorization by the European Union on September 18, 2014.

2.2 Regulatory History

The following is a summary of the regulatory history for Xultophy (NDA 208583) relevant to this review:

- 06/16/2015: Pre-NDA for insulin degludec/liraglutide (NDA 208583). FDA agrees with Novo Nordisk’s proposal to submit a REMS that has components of the Victoza approved REMS.
- 09/14/2015: FDA received a submission for Insulin degludec/liraglutide (NDA 208583) for the treatment of adults with type 2 diabetes mellitus.
- 11/12/2015: FDA granted conditional approval of proprietary name Xultophy.

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2 Insulin degludec/liraglutide (IDegLira) Introduction to Summary, dated June 24, 2015.
3 Insulin degludec/liraglutide (IDegLira) Clinical Overview, dated August 14, 2015.
5 FDAAA factor (D): The expected or actual duration of treatment with the drug.
6 Drugs at FDA.gov
• 03/15/2016: Mid-cycle communication letter sent to sponsor. FDA informed the sponsor that some revisions were necessary to their proposed REMS to align it with the recent Saxenda REMS modification approved on February 1, 2016.

• 04/29/2016: Late Cycle Meeting (LCM) background package sent by FDA requesting edits to be made to the Xultophy® REMS materials to align with the Saxenda® REMS (see comments included in section 8 of this review).

• 05/06/2016: Novo Nordisk submits a response to FDA’s REMS-related comments included in the LCM background package accepting all FDA’s proposed changes.

• 05/09/2016: LCM with sponsor.

• 05/11/2016: DRISK sent comments to the sponsor regarding REMS document.

• 05/24/2016: Endocrinologic and Metabolic Drugs Advisory Committee meeting. Panel members favored approval of Xultophy unanimously (vote 16:0 in favor) but recommended to focus the indication on a group of patients who would benefit the most from the use of this product.

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.7 According to the Centers of Disease Control and Prevention (CDC), diabetes affects over 29 million Americans (9.3 % of the US population).8 In 2012, there were 1.7 million new cases of diagnosed diabetes among people aged 20 years or older in the US.7 Diabetes may decrease life expectancy by 10-15 years and is the 7th leading cause of death in the US.7,9 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. The estimated cost of diabetes in the US (2012 data) is over $245 billion.7

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.10 However, the role of insulin resistance versus beta cell dysfunction differs among individuals. Glucose control tends to be more challenging over time.10 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.10

8 FDAAA factor (A): The estimated size of the population likely to use the drug involved.
9 FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.
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. 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. GLP-1 receptor agonists currently approved in the US include exenatide (twice-daily injection), liraglutide (once-daily injection), exenatide extended release (ER) (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 GLP1RA class (i.e., exenatide, exenatide extended release (ER), liraglutide, albiglutide, and dulaglutide) currently have, or have had at some point during the product’s lifecycle, a CP REMS to mitigate the risk of thyroid C-cell tumor and 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 below for a comparison between all FDA-approved GLP-1 agonists.

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<td>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 27 kg/m² or greater, or 30 kg/m² or greater in the presence of at least one weight-related comorbid condition.</td>
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<td>Box Warning Risk</td>
<td>No</td>
<td>Yes Thyroid C-cell tumor</td>
<td>Yes Thyroid C-cell tumor</td>
<td>Yes Thyroid C-cell tumor</td>
<td>Yes Thyroid C-cell tumor</td>
<td>Yes Thyroid C-cell tumor</td>
</tr>
<tr>
<td>W &amp; P</td>
<td>Acute pancreatitis</td>
<td>Thyroid C-cell tumor</td>
<td>Thyroid C-cell tumor</td>
<td>Thyroid C-cell tumor</td>
<td>Thyroid C-cell tumor</td>
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<tr>
<td></td>
<td>Hypoglycemia</td>
<td>Pancreatitis</td>
<td>Pancreatitis</td>
<td>Pancreatitis</td>
<td>Hypoglycemia</td>
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<tr>
<td></td>
<td>Renal impairment</td>
<td>Hypoglycemia</td>
<td>Hypoglycemia</td>
<td>Hypoglycemia</td>
<td>Renal impairment</td>
<td>Renal impairment</td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity</td>
<td>Renal impairment</td>
<td>Renal impairment</td>
<td>Renal impairment</td>
<td>Hypersensitivity</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal disease</td>
<td>Hypersensitivity</td>
<td>Hypersensitivity</td>
<td>Hypersensitivity</td>
<td>Heart rate increase</td>
<td>Heart rate increase</td>
</tr>
<tr>
<td></td>
<td>Immunogenicity</td>
<td>Gastrointestinal disease</td>
<td>Gastrointestinal disease</td>
<td>Gastrointestinal disease</td>
<td>Acute bladder disease</td>
<td>Acute bladder disease</td>
</tr>
<tr>
<td></td>
<td>Injection site reactions</td>
<td></td>
<td></td>
<td></td>
<td>Suicidal behavior/ideation</td>
<td>Suicidal behavior/ideation</td>
</tr>
<tr>
<td>REMS Risks</td>
<td>Pancreatitis</td>
<td>Thyroid C-cell tumor</td>
<td>Thyroid C-cell tumor</td>
<td>Thyroid C-cell tumor</td>
<td>Thyroid C-cell tumor</td>
<td>Thyroid C-cell tumor</td>
</tr>
<tr>
<td></td>
<td>Renal failure</td>
<td>Pancreatitis</td>
<td>Pancreatitis</td>
<td>Pancreatitis</td>
<td>Pancreatitis</td>
<td>Pancreatitis</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reference ID: 3954826
<table>
<thead>
<tr>
<th>Proprietary Generic</th>
<th>Byetta Exenatide</th>
<th>Bydurene Exenatide (ER)</th>
<th>Victoza Liraglutide</th>
<th>Saxenda Liraglutide</th>
<th>Tanzeum Albiglutide</th>
<th>Trulicity Dulaglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk Data Sources</strong></td>
<td>Thyroid C-cell tumor: N/A</td>
<td>Thyroid C-cell tumor: Labeling based on nonclinical data and liraglutide medullary thyroid carcinoma (MTC) postmarketing case reports.</td>
<td>Thyroid C-cell tumor labeling based on nonclinical data and liraglutide MTC postmarketing case reports.</td>
<td>Thyroid C-cell tumor labeling based on nonclinical data and liraglutide MTC postmarketing case reports.</td>
<td>Thyroid C-cell tumor labeling based on nonclinical data and liraglutide MTC postmarketing case reports.</td>
<td>Thyroid C-cell tumor labeling based on nonclinical data and liraglutide MTC postmarketing case reports.</td>
</tr>
<tr>
<td></td>
<td>Pancreatitis labeling based on Byetta’s postmarketing case reports.</td>
<td>Pancreatitis: 2.7 cases per 1000 patient-years in clinical trials. Signal supported by postmarketing case reports for liraglutide.</td>
<td>Pancreatitis: 0.3% in Saxenda-treated patients in clinical trials. Signal supported by postmarketing case reports for liraglutide.</td>
<td>Pancreatitis: 0.3% in Saxenda-treated patients in clinical trials. Signal supported by postmarketing case reports for liraglutide.</td>
<td>Pancreatitis: 0.3% in Tanzeum-treated patients in clinical trials.</td>
<td>Pancreatitis: 1.4 cases per 1000 Trulicity-treated patient-years in clinical trials.</td>
</tr>
<tr>
<td><strong>REMS Elements</strong></td>
<td>Medication Guide</td>
<td>Communication Plan Timetable</td>
<td>Communication Plan Timetable</td>
<td>Communication Plan Timetable</td>
<td>Communication Plan Timetable</td>
<td>Communication Plan Timetable</td>
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<td></td>
<td>Communication Plan Timetable</td>
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<td>Communication Plan Timetable</td>
<td>Communication Plan Timetable</td>
<td>Communication Plan Timetable</td>
</tr>
<tr>
<td><strong>REMS Assessment (most recent)</strong></td>
<td>Thyroid C-cell tumor: N/A</td>
<td>Thyroid C-cell tumor: Prescribers’ knowledge of thyroid C-cell tumors-related REMS messages was 74%.</td>
<td>Thyroid C-cell tumor: Prescribers’ knowledge of thyroid C-cell tumors-related REMS messages ranged from 83-85% respectively.</td>
<td>Thyroid C-cell tumor: Pending REMS Assessment Report review.</td>
<td>Thyroid C-cell tumor: 80% responded to 75% of the questions correctly.</td>
<td>Thyroid C-cell tumor: 86% of prescribers were aware of the potential risk of MTC.</td>
</tr>
<tr>
<td></td>
<td>Pancreatitis: Prescribers’ knowledge of pancreatitis-related REMS messages ranged between 93-99%. Time to 90% discontinuation decreased from 21 days to seven days.</td>
<td>Pancreatitis: Prescribers’ knowledge of pancreatitis-related REMS messages was 90%. REMS elimination: CP was completed and the REMS goals were met.</td>
<td>Percentage of prescribers answering correctly at least 3 out of 4 questions related to the risk of MTC ranged from 81-83%.</td>
<td>Pancreatitis: Prescribers’ knowledge of pancreatitis thyroid C-cell tumors-related REMS messages ranged from 83-91%. Percentage of prescribers answering correctly the 3 questions related to pancreatitis ranged from 72-81%).</td>
<td>Pancreatitis: 87% of respondents answered at least 75% of questions about the risk of pancreatitis correctly.</td>
<td>Pancreatitis: 95% of prescribers were aware of the risk of pancreatitis with Trulicity.</td>
</tr>
</tbody>
</table>

---

20 Naomi Redd, Pharm.D. DRISK. Bydurene REMS review dated April 9, 2015.
24 Eli Lilly. REMS Assessment Report for Trulicity, received by FDA on March 8, 2016.

Reference ID: 3954826
4 Benefit Assessment

The efficacy and safety of Xultophy was evaluated in 5 phase 3 trials: two pivotal trials (Trials 3697 and 3912) and three trials (Trials 3851, 3951, 3952) in different populations of subjects with type 2 diabetes mellitus defined by previous anti-diabetes treatment.3,4

- **Trial 3697** – Subjects inadequately controlled on oral antidiabetic agents who have not been previously treated with insulin or with a GLP-1 RA. Xultophy (833 subjects) vs. insulin degludec (413 subjects) and liraglutide (414 subjects). Open-labelled; randomized 2:1:1. Duration of 26 weeks plus a 26-week extension. The two main hypotheses of this study were superiority in HbA1c reduction with Xultophy relative to liraglutide and non-inferiority relative to insulin degludec. Additional endpoints included insulin dose, hypoglycaemia, body weight and prandial glycaemia. This trial showed statistically significant changes in the levels of HbA1c from baseline in favor of Xultophy (Xultophy vs. basal insulin -0.47 [−0.58;−0.36] <0.0001; Xultophy vs. liraglutide -0.64 [−0.75;−0.53] <0.0001).

- **Trial 3912** – Subjects inadequately controlled on oral antidiabetic agents and basal insulin. Xultophy (199) vs. insulin degludec (199). Double-blind; randomized 1:1. Duration of 26 weeks. This trial showed statistically significant changes in the levels of HbA1c from baseline in favor of Xultophy (Xultophy vs. basal insulin -1.05 [−1.25;−0.84] <0.0001).

- **Trial 3851** – Subjects inadequately controlled with a GLP-1 RA (liraglutide or exenatide) and oral antidiabetic agents. Xultophy (292 subjects) vs. GLP-1 RA (liraglutide/exenatide) (146). Open-label; randomized 2:1. Duration of 26 weeks. This trial showed statistically significant changes in the levels of HbA1c from baseline in favor of Xultophy (Xultophy vs. GLP-1 RA -0.94 [−1.11;−0.78] <0.0001).

- **Trial 3951** – Subjects inadequately controlled on basal insulin and oral antidiabetic agents (not previously treated with a GLP-1 RA). Xultophy (289 subjects) vs. placebo (146 subjects). Double-blind; randomization ratio 2:1. Duration of 26 weeks. This trial showed statistically significant changes in the levels of HbA1c from baseline in favor of Xultophy (Xultophy vs. placebo -1.02 [−1.18;−0.87] <0.0001).

- **Trial 3952** – Subjects inadequately controlled on basal insulin (insulin glargine) and oral antidiabetic agents (metformin). Xultophy (278 subjects) vs. insulin glargine (279 subjects). Open-label; randomized 1:1. Duration of 26 weeks. This trial showed statistically significant changes in the levels of HbA1c from baseline in favor of Xultophy (Xultophy vs. basal insulin -0.59 [−0.74;−0.45] <0.0001).

At the time when this review was completed, the assessment of the benefit and risks of Xultophy was ongoing. An advisory committee meeting was held on May 24, 2016 to discuss the Xultophy’s benefit:risk profile. The advisory panel voted unanimously in favor of the approval of Xultophy; however, the appropriate patient population to receive treatment with this product still needs to be defined.25

25 FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.
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 above. With the exception of Byetta (exenatide), all FDA approved GLP-1 RAs (Bydureon, Victoza, Saxenda, Tanzeum and Trulicity) have a boxed warning for the risk of thyroid C-cell tumors. Other important serious risks associated with the use of Xultophy include hypoglycemia, renal impairment, hypersensitivity and allergic reactions, and fluid retention and congestive heart failure with concomitant use of a peroxisome proliferator-activated receptor (PPAR)-gamma agonists.

5.1 Thyroid C-cell Tumor

No events of medullary thyroid cancer were identified in the Xultophy clinical development program. Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice. In addition, malignant thyroid C-cell carcinomas were detected in rats and mice. However, the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined. Therefore, it is unknown whether Xultophy will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans. There are postmarketing spontaneous case reports of MTC in patients treated with liraglutide but the data in these reports are insufficient to establish or exclude a causal relationship between MTC and liraglutide use in humans.4, 26

A recent review of the reports in the FDA Adverse Event Reporting System (FAERS) for medullary thyroid cancer (MTC) and acute pancreatitis (AP) reported for Victoza did not identify any new safety concerns related to MTC and pancreatitis. Error! Bookmark not defined. Error! Bookmark not defined.

5.2 Pancreatitis

Pancreatitis was reported in one patient on the insulin degludec group (non-treatment emergent) and in two events in the liraglutide group, of which one event occurred in a subject also diagnosed with pancreatic cancer stage IV.4

6 Expected Postmarket Use

Xultophy is expected to be prescribed by healthcare providers who treat patients with type 2 diabetes and prescribe other GLP1RAs (e.g., endocrinologist, internists, and primary care physicians). Xultophy 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 Evaluating the Need for a REMS

Consistent with prior FDA regulatory actions for liraglutide products (i.e., Victoza and Saxenda), DRISK and DMEP agree that a REMS with a communication plan is needed to ensure that the benefits of Xultophy outweighs its risk of thyroid C-cell tumor. Nonclinical data for liraglutide demonstrate a dose-

26 FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.
dependent and treatment duration-dependent association with thyroid C-cell tumors in rats and mice. Postmarketing data on Victoza-related MTC case reports are insufficient to establish or exclude a causal relationship between thyroid malignancies and exposure to liraglutide. Other FDA-approved products in the GLP-1 RA class (i.e., Bydureon, Victoza, Saxenda, Tanzeum, and Trulicity) 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.

Available prescriber survey data included in REMS assessment reports for Bydureon, Victoza, Tanzeum and Trulicity suggest that prescribers are knowledgeable about the risks of thyroid C-cell tumor and pancreatitis associated with these products, suggesting that the key risk messages have been effectively communicated to the relevant prescriber population (see Table 1). However, the direct impact of these CP REMS programs on the dissemination of the risk messages is unknown.

There are no postmarketing safety signals for GLP-1 RA products suggesting an increase in the reporting of thyroid C-cell tumors or pancreatitis beyond what is expected (see Table 1).

## 8 Risk Management Activities Proposed by the Applicant

The Applicant proposed a communication plan REMS for Xultophy similar to that of the Victoza REMS.

### 8.1 REVIEW OF APPLICANT’S PROPOSED REMS

#### 8.1.1 REMS Goals

The goal of the XULTOPHY REMS is to mitigate the potential risk of medullary thyroid carcinoma and the risk of acute pancreatitis (including necrotizing pancreatitis) associated with XULTOPHY by:

- Informing healthcare providers about the potential risk of medullary thyroid carcinoma associated with XULTOPHY
- Informing healthcare providers about the risk of acute pancreatitis (including necrotizing pancreatitis) associated with XULTOPHY.

**Reviewer’s Comments:** Agree.

#### 8.1.2 REMS Elements and Tools

The Applicant proposed a communication plan REMS for Xultophy including REMS Letters for healthcare providers and professional societies, a REMS Factsheet, REMS Slides, a plan for dissemination of REMS information at scientific meetings, a REMS website and a timetable for submission of assessments. The Applicant submitted the proposed REMS document, all REMS appended materials and a REMS Supporting Document. The application is complete.

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27 Bydureon REMS was eliminated in April 2015. See Table 1 included in this review.
28 Typically, prescriber knowledge assessment surveys included in REMS assessment reports are conducted in a convenience sample of prescribers (i.e., survey sample is not statistically representative of the actual prescriber population of these products).
Reviewer’s Comments: Following are comments regarding the Xultophy REMS and REMS materials. The documents appended to this review include tracked changes.

REMS Letters: Clarifying revisions in tracked changes to the REMS Letter for Healthcare Providers and REMS Letter for Professional Societies.

Factsheet: Clarifying changes to the REMS Factsheet to align the Factsheet with the Prescribing Information. See the revisions in tracked changes in the REMS Factsheet.

Slides: Presentation of Xultophy REMS information should reflect the information included in the presentation of the Saxenda REMS slides, instead of the Victoza REMS slides. For example, the first slide should contain only the information related to the definition and purpose of the REMS program. The next slide should contain information related to the potential risk of medullary thyroid carcinoma, including subheading for the Boxed Warning. Information about appropriate patient selection and patient management should follow on the next slides. The risk of acute pancreatitis should be its own slide with the information about appropriate patient selection and patient management following on another slide.

REMS Website: Remove the Important Safety Information from the top of the REMS webpage. As the Prescribing Information is also included at the top of the webpage, having this information is redundant and incomplete. The bullets appear too close together in the screenshot. Provide more space between the bullets.

REMS Document: The REMS Document proposed by Novo Nordisk was revised to be consistent with the recently approved modification to the Saxenda REMS Document and to reflect FDA’s current thinking about the description of relevant elements of the communication plan.

REMS Supporting Document: Revise REMS Supporting Document to reflect requested changes to the REMS, REMS message map for healthcare providers (see Table 2 below) and REMS materials.

The above comments on the REMS Letters, REMS Factsheet, REMS Slides and REMS Website were sent to Novo Nordisk on April 29, 2016. The sponsor made all the requested changes to the REMS materials and submitted an amendment to these REMS on May 6, 2016. DRISK reviewed the May 6, 2016 submission and concur with the changes proposed by the sponsor.

Comments on the REMS Document were sent to the sponsor on May 11, 2016. The sponsor submitted an amendment to the REMS (Seq. No. 0045) on May 20, 2016 addressing DRISK’s comments from May 11, 2016. The sponsor accepted most of DRISK reviewers’ comments and proposed some additional changes pertaining to: (1) follow up REMS letters, (2) “Medical Information” under the requirement for dissemination of REMS information at scientific meetings and (3) REMS website. In addition, the sponsor revised the REMS Supporting Document to reflect the changes made to the REMS document. DRISK reviewers concur with the changes proposed by the sponsor.

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8.1.3 Key REMS Messages

The sponsor proposed a REMS message map for healthcare providers, which is very similar to those approved for Victoza and Saxenda. See Table 2 below.

**Reviewer’s Comments:** The REMS elements and tools proposed for the Xultophy REMS are the same as those included in the Victoza REMS.

DRISK anticipates that, in conjunction with the other venues typically employed to communicate drug-related risk information (e.g., sales representative detailing, product prescribing information, company promotional materials, and other healthcare professionals), the Xultophy REMS elements and tools proposed by Novo Nordisk will contribute to the dissemination of the risk messages.

DRISK has made several changes to the proposed REMS message map to add clarity and make the risk messages more concise. See Table 2 below. The Xultophy REMS Supporting Document and materials must be revised to reflect these changes.

The REMS message map has been updated to better address what information should remain in the REMS materials to provide context to the key REMS messages regarding MTC and pancreatitis. It is important that the sponsor tests prescribers’ knowledge about each one of the key messages included in the REMS Message Map.

Therefore, we revised the REMS message map to reflect these changes. Nevertheless, this information should remain in the REMS materials to provide context to the key REMS messages regarding MTC and pancreatitis. It is important that the sponsor tests prescribers’ knowledge about each one of the key messages included in the REMS Message Map.
### TABLE 2: XULTOPHY® REMS MESSAGE MAP for HEALTHCARE PROVIDERS

<table>
<thead>
<tr>
<th>Message 1</th>
<th>Message 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potential Risk of Thyroid C-cell Tumors</strong></td>
<td><strong>Risk of Pancreatitis</strong></td>
</tr>
<tr>
<td>• Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice.</td>
<td>• Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis has been observed in patients treated with liraglutide.</td>
</tr>
<tr>
<td></td>
<td>• XULTOPHY® has not been studied sufficiently in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.</td>
</tr>
<tr>
<td>• XULTOPHY® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN2).</td>
<td>• After initiation of XULTOPHY®, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, and which may or may not be accomplished by vomiting). ▲ Discontinue XULTOPHY if pancreatitis is suspected. Do not restart if pancreatitis is confirmed.</td>
</tr>
<tr>
<td>• Counsel patients regarding the risk for MTC and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness). • Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with XULTOPHY®.</td>
<td>• Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.</td>
</tr>
</tbody>
</table>

### 8.1.4 REMS Assessment Plan

Xultophy REMS Assessment Plan is included in the REMS Supporting Document.

**Reviewer’s Comments:** The REMS Assessment Plan was revised to include an analysis of prescribers’ knowledge of the risks by individual risk domains, i.e., acute pancreatitis, medullary thyroid carcinoma.

Text was revised as follows (added text in blue):

b. **Evaluation of HCPs knowledge**
   i. An evaluation of HCPs’ knowledge of the potential risk of medullary thyroid carcinoma and the risk of acute pancreatitis (including necrotizing pancreatitis) associated with XULTOPHY®. Stratify results by type of HCP. Analyze and report survey results by key risk message domain (i.e., acute pancreatitis, medullary thyroid carcinoma).
8.2 OTHER PROPOSED RISK MANAGEMENT ACTIVITIES

Novo Nordisk proposed other activities to enhance the overall risk management plan for Xultophy. These include a safety surveillance study using the Optum Database (PMR 1583-6); additional serum calcitonin monitoring that will be done as part of a large cardiovascular outcomes trial (PMR 1583-9) and a case series registry that will be conducted to monitor the US population for incident cases of medullary thyroid carcinoma (PMR 1583-7).

We note that these other activities proposed by the applicant are outside of the scope of the REMS program and defer to DMEP and the Division of Epidemiology for review and input.

9 Conclusion & Recommendations

DRISK agrees with DMEP that the totality of the risks associated with Xultophy is serious and it is necessary for prescribers to understand these risks and the importance of monitoring for them. Based on the available nonclinical and postmarketing safety data regarding the risk of thyroid C-cell tumors, we agree that requiring a REMS consisting of a CP and a timetable for submission of REMS assessments is necessary to ensure that the benefits of Xultophy outweigh its risk of thyroid C-cell tumors.

Both liraglutide-containing products approved by FDA, i.e., Victoza and Saxenda, have a boxed warning for the risk of thyroid C-cell tumor and a communication plan (CP) REMS to mitigate this risk and the risk of pancreatitis. Other FDA-approved products in the GLP-1 RA class (i.e., exenatide ER, albiglutide, and dulaglutide) currently have, or have had a some point in their lifecycle, a CP REMS to mitigate the risk of thyroid C-cell tumor but also communicate the risk of pancreatitis associated with these products.

The applicant’s proposed REMS for Xultophy is similar to the Victoza and Saxenda REMS and includes a CP and a timetable for submission of assessments. Consistent with prior FDA regulatory actions for liraglutide products, DRISK and DMEP agree that a CP REMS is needed to ensure that the benefits of Xultophy outweigh it risk of thyroid C-cell tumor. The risk of pancreatitis will also be addressed by the REMS program to maintain consistency with the REMS for other GLP-1 RAs in the US market.

10 Comments for the Applicant

Following are comments regarding the Xultophy REMS Document, REMS materials and REMS Supporting Document. We remind you that the REMS materials must align with the final version of the Xultophy Prescribing Information. The documents appended to this communication include tracked changes.

1. REMS Document: FDA concurs with the changes you proposed on the REMS Document and REMS Supporting Document included in your submission received by the Agency on May 5, 2016.

2. REMS Supporting Document: Revise REMS Supporting Document to reflect requested changes to the REMS message map for healthcare providers (see Table 2 below) and REMS materials.

3. REMS Message Map: The REMS Message Map contains the key risk messages addressed by this REMS. The messages included in this map must be consistent with the product label and must be used to guide the development of all REMS-related documents, particularly, REMS assessment survey questions. FDA has made several changes to the proposed REMS Message Map to add clarity and make the risk messages more concise. See Table 1 below.
The REMS message map has been updated to better address what information should remain in the REMS materials to provide context to the key REMS messages regarding MTC and pancreatitis. It is important that the sponsor tests prescribers’ knowledge about each one of the key messages included in the REMS Message Map.

- [Image of a diagram showing four key messages]

Therefore, we revised the REMS message map to reflect these changes. Nevertheless, this information should remain in the REMS materials to provide context to the key REMS messages regarding MTC and pancreatitis. It is important that the sponsor tests prescribers’ knowledge about each one of the key messages included in the REMS Message Map.

The Xultophy REMS Supporting Document and materials should be revised to reflect these changes.

<table>
<thead>
<tr>
<th>TABLE 1: XULTOPHY® REMS MESSAGE MAP for HEALTHCARE PROVIDERS</th>
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</tr>
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<td>necrotizing pancreatitis has been observed in patients</td>
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<td>with a history of pancreatitis. Consider other antidiabetic</td>
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<td>therapies in patients with a history of pancreatitis.</td>
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<tr>
<td>observe patients carefully for signs and symptoms of</td>
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<td>pancreatitis (including persistent severe abdominal pain,</td>
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<td>sometimes radiating to the back, and which may or may not</td>
</tr>
<tr>
<td>be accomplished by vomiting). Discontinue XULTOPHY® if</td>
</tr>
<tr>
<td>pancreatitis is suspected. Do not restart if pancreatitis</td>
</tr>
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<td>is confirmed.</td>
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4. **REMS Assessment Plan**: The REMS Assessment Plan was revised to include an analysis of prescribers’ knowledge of the risks by individual risk domains, i.e., acute pancreatitis, medullary thyroid carcinoma. Text was revised as follows (added text in blue):

   c. Evaluation of HCPs knowledge

      i. An evaluation of HCPs’ knowledge of the potential risk of medullary thyroid carcinoma and the risk of acute pancreatitis (including necrotizing pancreatitis) associated with XULTOPHY®. Stratify results by type of HCP. **Analyze and report survey results by key risk message domain (i.e., acute pancreatitis, medullary thyroid carcinoma).**

### 11 Appendices

#### 11.1 **Materials Reviewed**

The following is a list of materials informing this review:


11.2 APPENDED DOCUMENTS

The following is a list of comments sent to the sponsor up to this time in the review cycle:

- Comments on the Xultophy REMS Document – sent to the sponsor on May 11, 2016 via email (COR-NDAIR-23(Labeling PMR/PMC Discussion Comments).
- Comments on the REMS appended materials – included in the Late-cycle meeting background package dated April 29, 2016.
  - REMS Letters
  - REMS Factsheet
  - REMS Slides
  - REMS Website
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/s/

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AMARILYS VEGA
07/13/2016

CYNTHIA L LACIVITA
07/14/2016
Concur