APPLICATION NUMBER:

208583Orig1s000

REMS
I. GOAL

The goal of the XULTOPHY® 100/3.6 REMS is to mitigate the potential risk of medullary thyroid carcinoma and the risk of acute pancreatitis (including necrotizing pancreatitis) associated with XULTOPHY® 100/3.6 by:

- Informing healthcare providers about the potential risk of medullary thyroid carcinoma associated with XULTOPHY® 100/3.6.
- Informing healthcare providers about the risk of acute pancreatitis (including necrotizing pancreatitis) associated with XULTOPHY® 100/3.6.

II. REMS ELEMENTS

A. Communication Plan

Novo Nordisk must implement the following communication plan to healthcare providers (HCPs) likely to prescribe XULTOPHY® 100/3.6. The communication plan must include:

1. REMS Letters

Novo Nordisk must send a REMS Letter for Healthcare Providers and a REMS Letter for Professional Societies within 60 calendar days of approval of the REMS. Novo Nordisk must send a second mailing 12 months from the date of the REMS approval. The REMS Letters must address the potential risk of medullary thyroid tumors and the risk of acute pancreatitis.

Mail must be the primary method to disseminate the REMS Letters. If the mailed letter is undeliverable, Novo Nordisk must use available resources to obtain updated address information and send a second letter via US mail within 45 calendar days. If the proper address cannot be obtained, the communication will not be sent again.

Novo Nordisk must make the REMS Letter for Healthcare Providers available via a link from the XULTOPHY® 100/3.6 REMS website, through Novo Nordisk’s Medical Information Department upon request, and from Novo Nordisk field based sales and/or medical representatives upon request for one year after approval of the REMS.

A copy of or a link to the US Prescribing Information, Medication Guide and REMS Factsheet must accompany the REMS Letters.
a. REMS Letter for Healthcare Providers

The intended audience for the REMS Letter for Healthcare Providers must be physicians, nurse practitioners, and physicians’ assistants in the specialties of endocrinology, internal medicine and family practice.

b. REMS Letter for Professional Societies

The intended audience for the REMS Letter for Professional Societies must be the following professional societies and organizations. Novo Nordisk must request that the letter or content be provided to the societies’ members:

- American College of Physicians
- American Medical Association
- American Academy of Family Physicians
- American College of Osteopathic Family Physicians
- American College of Clinical Pharmacy
- American Pharmacists Association
- American Society of Health-System Pharmacists
- American Academy of Nurse Practitioners
- American Association of Clinical Endocrinologists
- Endocrine Society
- American Diabetes Association
- American Association of Diabetes Educators
- American Academy of Physician Assistants
- Association of Managed Care Pharmacy
- National Association of Managed Care Physicians

2. REMS Factsheet

A REMS Factsheet must be made available to healthcare providers and disseminated through Novo Nordisk field based sales or medical representatives during the initial healthcare providers discussion within the first 18 months after approval of this REMS. Novo Nordisk field based sales or medical representatives must orally review each risk message contained in the REMS Factsheet.

3. REMS Slides

The REMS Slides must provide information about the potential risk of medullary thyroid carcinoma and the risk of acute pancreatitis (including necrotizing pancreatitis) associated with XULTOPHY® 100/3.6. The REMS Slides must be available at the XULTOPHY® 100/3.6 REMS website within 60 calendar days of REMS approval and must be part of a slide deck used at Novo Nordisk sponsored speaker training and promotional programs for the first 3 years after approval of the REMS.
4. **Dissemination of REMS information at scientific meetings**

The XULTOPHY® 100/3.6 *REMS Factsheet* must be prominently displayed and disseminated together with responses to medical information requests at all scientific meetings where Novo Nordisk Medical Information has a presence (e.g., booth) for the first 3 years after approval of the REMS.

5. **REMS Website**

The XULTOPHY® 100/3.6 REMS Program Website ([www.xultophy10036pro.com/REMS](http://www.xultophy10036pro.com/REMS)) must continue for 3 years. The REMS website must include the option to print the currently approved Prescribing Information, Medication Guide, *REMS Letter for Healthcare Providers*, *REMS Factsheet* and the *REMS Slides*. The XULTOPHY® 100/3.6 website for healthcare professionals ([www.xultophy10036pro.com](http://www.xultophy10036pro.com)) and the consumer website ([www.xultophy10036.com](http://www.xultophy10036.com)) must include a prominent REMS-specific link to the XULTOPHY® 100/3.6 REMS Program Website ([www.xultophy10036pro.com/REMS](http://www.xultophy10036pro.com/REMS)).

The following are part of the REMS and are appended:

- *REMS Letter for Healthcare Providers*
- *REMS Letter for Professional Societies*
- *REMS Factsheet*
- *REMS Slides*
- XULTOPHY® 100/3.6 REMS Website (landing page)

**B. Timetable for Submission of Assessments**

Novo Nordisk must submit REMS Assessments to FDA at 18 months, 3 years and 7 years from the date of the initial approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Novo Nordisk must submit each assessment so that it will be received by the FDA on or before the due date.
Important Safety Notice

The FDA has required this notice as part of the XULTOPHY® 100/3.6 REMS (Risk Evaluation and Mitigation Strategy) to inform healthcare providers about the following serious risks of Xultophy® 100/3.6 (insulin degludec/liraglutide):

Potential Risk of Medullary Thyroid Carcinoma

- Liraglutide, one of the components of XULTOPHY® 100/3.6, causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether XULTOPHY® 100/3.6 causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined.

- Cases of MTC in patients treated with liraglutide have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and liraglutide use in humans.

Risk of Acute Pancreatitis

- Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis has been observed in patients treated with liraglutide.

Because of these risks, XULTOPHY® 100/3.6 is not recommended as a first-line therapy for patients inadequately controlled on diet and exercise.

A non-promotional factsheet, reviewed by the FDA, with more detailed safety information about these risks is enclosed. Please visit www.xultophy10036pro.com/REMS for more information about the XULTOPHY® 100/3.6 REMS program.

Indication: XULTOPHY® 100/3.6 is a combination of insulin degludec and liraglutide, 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).
This letter does not contain the complete safety profile for XULTOPHY® 100/3.6. Please see the Prescribing Information, including Boxed Warning, and Medication Guide, which are enclosed with this letter.

**Reporting Adverse Events**

You are encouraged to report negative side effects of prescription drugs to the FDA. Please contact Novo Nordisk at 1-800-727-6500 or contact the FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

Sincerely,

Todd Hobbs, M.D.
Vice President, North America, Chief Medical Officer, Novo Nordisk

Enclosure: XULTOPHY® 100/3.6 REMS: FDA Required Safety Information
XULTOPHY® 100/3.6 Full Prescribing Information       XULTOPHY® 100/3.6 Medication Guide
Important Safety Notice

The FDA has required Novo Nordisk to distribute this safety notice to your organization as part of their XULTOPHY® 100/3.6 REMS (Risk Evaluation and Mitigation Strategy) program. We request that you provide the letter or the risk information included in this letter and enclosed factsheet to your membership to inform your members about the following serious risks of XULTOPHY® 100/3.6:

Potential Risk of Medullary Thyroid Carcinoma

- Liraglutide, one of the components of XULTOPHY® 100/3.6, causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether XULTOPHY® 100/3.6 causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined.

- Cases of MTC in patients treated with liraglutide have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and liraglutide use in humans.

Risk of Acute Pancreatitis

- Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis has been observed in patients treated with liraglutide.

Because of these risks, XULTOPHY® 100/3.6 is not recommended as a first-line therapy for patients inadequately controlled on diet and exercise.

A non-promotional factsheet, reviewed by the FDA, with more detailed safety information about these risks is enclosed. Please visit www.xultophy10036pro.com/REMS for more information about the XULTOPHY® 100/3.6 REMS program.

Indication: XULTOPHY® 100/3.6 is a combination of insulin degludec and liraglutide, 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).
This letter does not contain the complete safety profile for XULTOPHY® 100/3.6. Please see the Prescribing Information, including Boxed Warning, and Medication Guide, which are enclosed with this letter.

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Sincerely,

Todd Hobbs, M.D.
Vice President, North America, Chief Medical Officer, Novo Nordisk
Enclosure: XULTOPHY® 100/3.6 REMS: FDA Required Safety Information
XULTOPHY® 100/3.6 Full Prescribing Information  XULTOPHY® 100/3.6 Medication Guide
FDA Required REMS* Safety Information

- Potential Risk of Medullary Thyroid Carcinoma
- Risk of Acute Pancreatitis

Potential Risk of Medullary Thyroid Carcinoma

**BOXED WARNING - Risk of Thyroid C-Cell Tumors**

- Liraglutide, one of the components of XULTOPHY® 100/3.6, causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether XULTOPHY® 100/3.6 causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined.

- **Counsel patients** regarding the risk of MTC and the symptoms of thyroid tumors (e.g., *mass in the neck, dysphagia, dyspnea or persistent hoarseness*). Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

- Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with XULTOPHY® 100/3.6. Such monitoring may increase the risk of unnecessary procedures, due to the low specificity of serum calcitonin testing for MTC and a high background incidence of thyroid disease. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated.

* The information presented in this box does not represent the complete Boxed Warning. Please see the Prescribing Information.
Risk of Acute Pancreatitis

- Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis has been observed in patients treated with liraglutide.
- After initiation of XULTOPHY® 100/3.6, 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 accompanied by vomiting).
- Discontinue XULTOPHY® 100/3.6 if pancreatitis is suspected. Do not restart if pancreatitis is confirmed.
- Consider other antidiabetic therapies in patients with a history of pancreatitis.
- XULTOPHY® 100/3.6 has not been studied in patients with a history of pancreatitis.

**Indication:** XULTOPHY® 100/3.6 is a combination of insulin degludec and liraglutide, 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).

XULTOPHY® 100/3.6 is not recommended as a first-line therapy for patients inadequately controlled on diet and exercise.

* What is the XULTOPHY® 100/3.6 REMS?

- A REMS (Risk Evaluation and Mitigation Strategy) is a program required by the FDA to manage known or potential serious risks associated with a drug product. FDA has determined that a REMS is necessary to ensure that the benefits of XULTOPHY® 100/3.6 outweigh the potential risk of medullary thyroid carcinoma and the risk of acute pancreatitis. Novo Nordisk Inc. has established an informational program for healthcare professionals to help minimize these risks. This factsheet is required by the FDA as part of the XULTOPHY® 100/3.6 REMS program.
- Please visit [www.xultophy10036pro.com/REMS](http://www.xultophy10036pro.com/REMS) for further information.

**Reporting Adverse Events:**

To report adverse events contact:

- Novo Nordisk at 1-800-727-6500 and/or
- FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

*This factsheet does not contain the complete safety profile for XULTOPHY® 100/3.6. Please refer to the Prescribing Information, including Boxed Warning, for further information.* If you have any questions about these materials, please call the Novo Nordisk Customer Care Center at 1-800-727-6500.
A REMS (Risk Evaluation and Mitigation Strategy) is a strategy required by the Food and Drug Administration (FDA) to manage known or potential serious risks associated with a drug product to ensure the benefits of a drug outweigh its risks.

The purpose of the XULTOPHY® 100/3.6 REMS is to inform healthcare providers of the following serious risks associated with XULTOPHY® 100/3.6:

- Potential Risk of Medullary Thyroid Carcinoma
- Risk of Acute Pancreatitis

Please see Important Safety Information in this presentation. Please see Prescribing Information.
Potential Risk of Medullary Thyroid Carcinoma

BOXED WARNING: RISK OF THYROID C-CELL TUMORS

- Liraglutide, one of the components of XULTOPHY® 100/3.6, causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice.
- It is unknown whether XULTOPHY® 100/3.6 causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined.

Please see Important Safety Information in this presentation.  
Please see Prescribing Information.
Potential Risk of Medullary Thyroid Carcinoma (2)

- Cases of MTC in patients treated with liraglutide have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and liraglutide use in humans.
Potential Risk of Medullary Thyroid Carcinoma (3)

**Appropriate Patient Selection**

- XULTOPHY® 100/3.6 is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN2).

- Xultophy® 100/3.6 is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.
**Patient Management**

- **Counsel patients** regarding the risk for MTC and inform them of symptoms of thyroid tumors (e.g., *mass in the neck, dysphagia, persistent hoarseness*).

- **Instruct patients** to contact their healthcare provider promptly if these symptoms occur.

- Patients with thyroid nodules noted on physical examination or neck imaging should be further evaluated.

- Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value in patients treated with XULTOPHY® 100/3.6.

- If serum calcitonin is measured and found to be elevated, the patient should be further evaluated.

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Please see Important Safety Information in this presentation. Please see Prescribing Information.
Risk of Acute Pancreatitis

- Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with liraglutide.
**Risk of Acute Pancreatitis (2)**

**Appropriate Patient Selection**

- XULTOPHY® 100/3.6 has not been studied sufficiently in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.

**Patient Management**

- After initiation of XULTOPHY® 100/3.6, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis.
- **Counsel patients** to contact their healthcare provider promptly if they experience symptoms of pancreatitis (including **persistent severe abdominal pain, sometimes radiating to the back, and which may or may not be accompanied by vomiting**).
- Discontinue XULTOPHY® 100/3.6 if pancreatitis is suspected.
- Do not restart if pancreatitis is confirmed.

*Please see Important Safety Information in this presentation.*

*Please see Prescribing Information.*
XULTOPHY® 100/3.6 REMS PROGRAM
A REMS (Risk Evaluation and Mitigation Strategy) is a strategy required by the Food and Drug Administration (FDA) to manage known or potential serious risks associated with a drug product to ensure the benefits of a drug outweigh its risks.

The purpose of the XULTOPHY® 100/3.6 REMS is to inform healthcare providers about the following serious risks:

Potential Risk of Medullary Thyroid Carcinoma
  • Liraglutide, one of the components of XULTOPHY® 100/3.6, causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice.
  It is unknown whether XULTOPHY® 100/3.6 causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined.
  • Cases of MTC in patients treated with liraglutide have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and liraglutide use in humans.

Risk of Acute Pancreatitis
  • Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis has been observed in patients treated with liraglutide.

Please see the non-promotional XULTOPHY® 100/3.6 REMS Factsheet for Prescribers, reviewed by the FDA, for further information on these risks.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEAN-MARC P GUETTIER
11/21/2016