

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125469Orig1s000

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

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: BLA 125469
Products: TRULICITY (dulaglutide) injection, 1.5 mg/0.5 ml, 0.75 mg/0.5 ml
APPLICANT: (b) (4)
FROM: Jennifer Rodriguez Pippins, M.D., M.P.H.
DATE: September 10, 2014

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 TRULICITY (dulaglutide) to ensure that the benefits of the drug outweigh:

- The potential risk of medullary thyroid carcinoma identified in non-clinical studies of TRULICITY (dulaglutide) and other glucagon-like peptide (GLP)-1 receptor agonists; and
- The risk of pancreatitis identified in the clinical trial data and in post-marketing reports for other approved (GLP)-1 receptor agonists. Cases of pancreatitis have also been described in association with TRULICITY (dulaglutide) during clinical trials. In reaching this determination, we considered the following:

A. In 2010, diabetes affected 25.8 million people in the United States, of which 18.8 million were diagnosed and 7.0 million were undiagnosed.¹ Type 2 diabetes is thought to account for 90 to 95 percent of all diagnosed cases in adults.² In 2012, approximately 670,000

¹ <http://www.cdc.gov/diabetes/pubs/factsheet11/fastfacts.htm>; accessed March 28, 2014.

² <http://ndep.nih.gov/diabetes-facts/>; accessed March 28, 2014.

patients in the United States filled prescriptions in retail pharmacies for (GLP)-1 receptor agonists.³

- 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. TRULICITY (dulaglutide) has been shown to achieve a mean placebo-adjusted reduction in hemoglobin A1c over 26 weeks of approximately 1-1.2% in trials comparing dulaglutide to placebo, with metformin as background therapy. Some of the complications listed above can be prevented or delayed with good glycemic control. TRULICITY (dulaglutide) is an option for those individuals who are inadequately treated with lifestyle modification and other anti-diabetic therapies.
- D. The expected duration of therapy is over a patient's lifetime.
- E. In addition to the most serious risks of medullary thyroid carcinoma and pancreatitis, TRULICITY (dulaglutide) also has the following risks: serious hypoglycemia when used with an insulin secretagogue (e.g., a sulfonylurea) or insulin, hypersensitivity, renal impairment, and gastrointestinal adverse events such as nausea, diarrhea, and vomiting.
- F. TRULICITY (dulaglutide) 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.

³ Hampp C, Borders-Hemphil V, Money DG, Wysowski DK. Use of Antidiabetic Drugs in the U.S., 2003-2012. *Diabetes Care*. 2014 Mar 12. [Epub ahead of print].

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/s/

JENNIFER R PIPPINS
09/18/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: September 17, 2014

Reviewers: Naomi Redd, PharmD, Risk Management Analyst
DRISK
Kate Heinrich Oswell, MA, Senior Health Communications Analyst, DRISK

Team Leader: Doris Auth, PharmD, Acting Team Leader
DRISK

Division Director: Cynthia LaCivita, PharmD, Acting Division Director,
DRISK

Subject: Review of the amended proposed REMS September 17, 2014

Drug Name(s): dulaglutide (Trulicity®)

Therapeutic Class: Glucagon-like peptide 1 (GLP-1) receptor agonist

Dosage and Route: 1.5mg/0.5ml, and 0.75mg/0.5ml subcutaneous

Application Type/Number: BLA 125469

Applicant/sponsor: Eli Lilly and Company

OSE RCM #: 2013-2184

***** This document contains proprietary and confidential information that should not be released to the public. *****

1 INTRODUCTION

This review provides comments on the amended proposed risk evaluation and mitigation strategy (REMS) for dulaglutide submitted on September 17, 2014. Eli Lilly is seeking approval for dulaglutide as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). Revisions to Eli Lilly's amended REMS are based on labeling negotiations on September 17, 2014.

As in alignment with other drugs in the glucagon-like peptide-1 (GLP-1) receptor agonists class, in addition to the wide prescriber population likely to prescribe and dispense dulaglutide, DRISK has determined that a communication plan (CP) REMS for dulaglutide is necessary to ensure the benefits of dulaglutide outweigh the risk of pancreatitis and potential risk of medullary thyroid carcinoma (MTC).

2 MATERIALS REVIEWED

- Eli Lilly's proposed amended CP REMS submitted September 17, 2014
- Draft of near final label September 17, 2014

Previous DRISK reviews related to the original submission

- May 30, 2014 – DRISK REMS Review for Dulaglutide BLA 125469; Redd N.
- August 25, 2014 – DRISK REMS Review for Dulaglutide BLA 125469; Redd N.
- September 11, 2014 – DRISK REMS Review for Dulaglutide BLA 125469; Redd N.

3 RESULTS OF REVIEW

The Sponsor accepted the revisions received from the Agency on September 15, 2014. Clarification regarding when the REMS letters would be sent after approval were made to the REMS and REMS supporting document which include: within 60 days of product approval, and then again 12 months after the date of product approval. (b) (4)

These changes were updated in the REMS and all REMS materials and supporting document. In addition, the REMS Factsheet was edited to be two pages by removing the page header numbers and slightly decreasing the size of the Trulicity logo. Labeling negotiations at this time are still ongoing describing hypersensitivity and describing use of monotherapy in the clinical trial section, and are not expected to impact the REMS.

3.1 REMS

The REMS to be approved is a communication plan with the following components:

Goal:

The goal of the TRULICITY REMS is to mitigate the potential risk of medullary thyroid carcinoma and the risk of pancreatitis associated with the use of TRULICITY by:

- Informing healthcare providers (HCPs) about the potential risk of medullary thyroid carcinoma associated with TRULICITY.
- Informing HCPs about the risk of pancreatitis associated with TRULICITY.

Communication Pieces

The communication pieces include REMS Letters for Healthcare Providers, REMS letters for Professional Societies, and a REMS Factsheet to accompany the letters and to be distributed by Eli Lilly representatives in visits to discuss Trulicity. These materials will be on the Trulicity REMS website, which will be maintained for the duration of the REMS.

Timetable for Submission of Assessments

The sponsor will submit REMS Assessments to FDA at 18 months, 3 years, and 7 years from the date of the REMS approval.

3.2 REMS ASSESSMENT PLAN

The REMS assessment plan is as follows:

1. REMS communication plan activities:
 - a. Number of healthcare providers (HCPs) and professional societies targeted by the REMS.
 - b. Number of REMS letters sent to HCPs and professional societies via email, standard mail, and facsimile, and the dates the letters were sent. Include the number of letters sent via standard mail because the HCP did not have an email address, and the number sent because the email was undeliverable. For letters sent via email, include the number of letters successfully delivered, and the number of email letters opened by the recipients.
 - c. Number of REMS Factsheets distributed to HCPs during the 12 months after product launch.
 - d. Date when REMS website went live and number of total and unique site visits during the assessment period.

2. Evaluation of HCPs' understanding of:
 - a. The potential risk of medullary thyroid carcinoma (MTC)
 - b. The risk of pancreatitis
 - c. The need for prompt evaluation of patients who develop symptoms suggestive of pancreatitis
 - d. Identification and treatment of pancreatitis after initiation of dulaglutide
 - e. Appropriate dulaglutide patient population characteristics
3. Safety surveillance
 - a. Dulaglutide utilization information including, but not limited to, indication and type of HCP (i.e., endocrinologist, general practitioner, internist, etc.)
 - b. Evaluation and post-marketing case reports of pancreatitis
 - c. Evaluation and post-marketing case reports of medullary thyroid carcinoma (MTC)
 - d. Any other relevant data and analysis employed to assess if the dulaglutide REMS is meeting its goals
 - e. The evaluation shall include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or elements should be modified. If a REMS modification is needed, provide an overview of the impact of the REMS modification on stakeholders and any additional evaluations needed as part of the REMS assessment plan to assess the impact of the proposed REMS modification.

4 CONCLUSION AND RECOMMENDATIONS

DRISK finds the REMS submission acceptable, and the REMS can be approved.

ATTACHMENTS

Trulicity REMS

Trulicity REMS Letters

Trulicity REMS Factsheet

Trulicity REMS website

Initial REMS approval: 09/2014

BLA 125469 TRULICITY™
(Dulaglutide)
Glucagon-like Peptide-1 (GLP-1) Receptor Agonist

Eli Lilly and Company
Lilly Corporate Center, Indianapolis, Indiana 46285
Telephone: 317-276-2000

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL

The goal of the TRULICITY REMS is to mitigate the potential risk of medullary thyroid carcinoma and the risk of pancreatitis associated with the use of TRULICITY by:

- Informing healthcare providers (HCPs) about the potential risk of medullary thyroid carcinoma associated with TRULICITY.
- Informing HCPs about the risk of pancreatitis associated with TRULICITY.

II. REMS Elements

A. Communication Plan

Eli Lilly and Company (Lilly) will implement the following communication plan to HCPs likely to prescribe TRULICITY. The communication plan will include:

1. REMS Letters

Lilly will send a *REMS Letter for Healthcare Providers* and a *REMS Letter for Professional Societies* within 60 days of product approval and again after 12 months of product approval. The REMS Letters will address the potential risk of medullary thyroid carcinoma and the risk of pancreatitis.

Distribution of the REMS Letters will be via electronic mail (email). If the email or fax is marked as undeliverable, a follow-up hard copy of the REMS Letter will be sent within 30 days of the undeliverable date. For those HCPs who do not prefer to receive electronic communications and for those HCPs whose e-mail and/or fax communications fail, a direct mail REMS Letter will be sent.

A copy of (or a link to) the Prescribing Information (PI), Medication Guide, and REMS Factsheet will accompany the REMS Letters.

REMS Letter for Healthcare Providers

The intended audience for the *REMS Letter for Healthcare Providers* will be endocrinologists as well as those HCPs (including physicians in internal medicine and family practice, nurse practitioners, and physician assistants) who have prescribed a glucagon-like peptide-1 (GLP-1) receptor agonist in the 12 months prior to dissemination of the letter.

The *REMS Letter for Healthcare Providers* will also be available via a link from the TRULICITY REMS website, through The Lilly Answers Center, and from Eli Lilly sales and medical representatives for the duration of the REMS.

REMS Letter for Professional Societies

Lilly will send the *REMS Letter for Professional Societies* to the leadership of the following professional societies and organizations and will request that the letter or the content be provided to their membership:

- 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 for HCPs will be distributed with the REMS Letters and will be made available to HCPs through Lilly's sales and medical representatives during the initial product discussion of TRULICITY with all HCPs visited during the first 12 months after approval of this REMS.

The REMS Factsheet for HCPs is part of the REMS and is appended.

3. REMS Website

The TRULICITY REMS website for healthcare professionals (www.TRULICITYREMS.com) will continue for the duration of the REMS and will provide access to downloadable versions of all the REMS materials, the Prescribing Information, and Medication Guide. The TRULICITY product website will include a link to the TRULICITY REMS website.

The following are part of the TRULICITY REMS and are appended:

- The *REMS Letter for Healthcare Providers* (print and email versions)
- The *REMS Letter for Professional Societies* (print and email versions)
- The REMS Factsheet
- The TRULICITY REMS Website

The TRULICITY REMS webpage is part of the REMS and is appended.

B. Timetable for Submission of Assessments

Lilly will submit REMS assessments to the Food and Drug Administration (FDA) at 18 months, 3 years, and 7 years from the date of the initial approval of the REMS. The reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment time interval. Lilly will submit each assessment so that it will be received by the FDA on or before the due date.



TRULICITY REMS

FDA Required REMS Safety Information

- **Potential Risk of Medullary Thyroid Carcinoma (MTC)**
- **Risk of Pancreatitis**

Important Safety Notice

The FDA has required this safety notice as part of the TRULICITY REMS (Risk Evaluation and Mitigation Strategy) to inform healthcare providers about the following **serious risks of TRULICITY (dulaglutide)**:

- **Potential Risk of Medullary Thyroid Carcinoma (MTC).** Thyroid C-cell tumors have been observed in rodent studies with glucagon-like peptide (GLP-1) receptor agonists. It is unknown whether TRULICITY causes thyroid C-cell tumors, including MTC, in humans. Counsel patients regarding the risk of MTC and the symptoms of thyroid tumors.
- **Risk of Pancreatitis.** Pancreatitis has been reported with the use of GLP-1 receptor agonists. Cases of pancreatitis have been described in association with TRULICITY during clinical trials. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. Consider other antidiabetic therapies in patients with a history of pancreatitis.

Because of these risks, TRULICITY is not recommended as first-line therapy for patients with type 2 diabetes mellitus inadequately controlled on diet and exercise.

A non-promotional factsheet, reviewed by the FDA, with more detailed safety information about these risks is enclosed.

Indication: TRULICITY is a GLP-1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Please visit www.TRULICITYREMS.com for more information.

This letter does not contain the complete safety information for TRULICITY. Please see the enclosed Prescribing Information and Medication Guide.

Reporting Adverse Events

You are encouraged to report negative side effects of prescription drugs to Eli Lilly and Company (the Sponsor) at 1-800-LillyRx (1-800-545-5979) and/or the FDA at www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please contact The Lilly Answers Center at 1-800-545-5979 with any questions about the information in this letter or the safe and effective use of TRULICITY.

Sincerely,

Robert W. Baker, M.D.
Vice President, Global Patient Safety
Eli Lilly and Company



TRULICITY REMS

FDA Required REMS Safety Information

- **Potential Risk of Medullary Thyroid Carcinoma (MTC)**
- **Risk of Pancreatitis**

Important Safety Notice

The FDA has required Eli Lilly and Company to distribute this safety notice as part of the TRULICITY REMS (Risk Evaluation and Mitigation Strategy) program. We request that you inform your members about the following **serious risks of TRULICITY (dulaglutide)**:

- **Potential Risk of Medullary Thyroid Carcinoma (MTC).** Thyroid C-cell tumors have been observed in rodent studies with glucagon-like peptide (GLP-1) receptor agonists. It is unknown whether TRULICITY causes thyroid C-cell tumors, including MTC, in humans. Counsel patients regarding the risk of MTC and the symptoms of thyroid tumors.
- **Risk of Pancreatitis.** Pancreatitis has been reported with the use of GLP-1 receptor agonists. Cases of pancreatitis have been described in association with TRULICITY during clinical trials. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. Consider other antidiabetic therapies in patients with history of pancreatitis.

Because of these risks, TRULICITY is not recommended as first-line therapy for patients with type 2 diabetes mellitus inadequately controlled on diet and exercise.

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Indication: TRULICITY is a GLP-1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

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Please contact The Lilly Answers Center at 1-800-545-5979 with any questions about the information in this letter or the safe and effective use of TRULICITY.

Sincerely,

Robert W. Baker, M.D.
Vice President, Global Patient Safety
Eli Lilly and Company

From: Eli Lilly and Company
To: Healthcare Providers
Subject: Potential Risk of Medullary Thyroid Carcinoma and Risk of Pancreatitis with Trulicity (Dulaglutide)



TRULICITY REMS

FDA Required REMS Safety Information

- Potential Risk of Medullary Thyroid Carcinoma (MTC)
- Risk of Pancreatitis

Important Safety Notice

The FDA has required this safety notice as part of the TRULICITY REMS (Risk Evaluation and Mitigation Strategy) to inform healthcare providers about the following **serious risks of TRULICITY (dulaglutide)**:

- **Potential Risk of Medullary Thyroid Carcinoma (MTC).** Thyroid C-cell tumors have been observed in rodent studies with glucagon-like peptide (GLP-1) receptor agonists. It is unknown whether TRULICITY causes thyroid C-cell tumors, including MTC, in humans. Counsel patients regarding the risk of MTC and the symptoms of thyroid tumors.
- **Risk of Pancreatitis.** Pancreatitis has been reported with the use of GLP-1 receptor agonists. Cases of pancreatitis have been described in association with TRULICITY during clinical trials. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. Consider other antidiabetic therapies in patients with a history of pancreatitis.

Because of these risks, TRULICITY is not recommended as first-line therapy for patients with type 2 diabetes mellitus inadequately controlled on diet and exercise.

A non-promotional factsheet, reviewed by the FDA, with more detailed safety information about these risks is available at www.TRULICITYREMS.com.

Please visit www.TRULICITYREMS.com for more information.

Indication: TRULICITY is a GLP-1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

This letter does not contain the complete safety information for TRULICITY. To review the Prescribing Information and Medication Guide, see links below:

Prescribing Information

[Active link to be included in communication](#)

Medication Guide

[Active link to be included in communication](#)

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Sincerely,

Robert W. Baker, M.D.
Vice President, Global Patient Safety
Eli Lilly and Company

From: Eli Lilly and Company
To: Professional Society
Subject: Potential Risk of Medullary Thyroid Carcinoma and Risk of Pancreatitis with Trulicity (Dulaglutide)



TRULICITY REMS

FDA Required REMS Safety Information

- Potential Risk of Medullary Thyroid Carcinoma (MTC)
- Risk of Pancreatitis

Important Safety Notice

The FDA has required Eli Lilly and Company to distribute this safety notice to your organization as part of the TRULICITY REMS (Risk Evaluation and Mitigation Strategy) program.

We request that you inform your members about the following **serious risks of TRULICITY (dulaglutide)**:

- **Potential Risk of Medullary Thyroid Carcinoma (MTC).** Thyroid C-cell tumors have been observed in rodent studies with glucagon-like peptide (GLP-1) receptor agonists. It is unknown whether TRULICITY causes thyroid C-cell tumors, including MTC, in humans. Counsel patients regarding the risk of MTC and the symptoms of thyroid tumors.
- **Risk of Pancreatitis.** Pancreatitis has been reported with the use of GLP-1 receptor agonists. Cases of pancreatitis have been described in association with TRULICITY during clinical trials. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. Consider other antidiabetic therapies in patients with a history of pancreatitis.

Because of these risks, TRULICITY is not recommended as first-line therapy for patients with type 2 diabetes mellitus inadequately controlled on diet and exercise.

A non-promotional factsheet, reviewed by the FDA, with more detailed safety information about these risks is available at www.TRULICITYREMS.com.

Please visit www.TRULICITYREMS.com for more information.

Indication: TRULICITY is a GLP-1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

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[Active link to be included in communication](#)

Medication Guide

[Active link to be included in communication](#)

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Sincerely,

Robert W. Baker, M.D.
Vice President, Global Patient Safety
Eli Lilly and Company



TRULICITY REMS (Risk Evaluation and Mitigation Strategy)

FDA Required TRULICITY REMS Safety Information

- **Potential Risk of Medullary Thyroid Carcinoma (MTC)**
- **Risk of Pancreatitis**

Potential Risk of Medullary Thyroid Carcinoma (MTC)

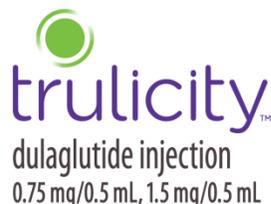
BOXED WARNING- Risk of Thyroid C-Cell Tumors

- Dulaglutide causes thyroid C-cell tumors in rats. It is unknown whether TRULICITY causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance could not be determined from clinical or nonclinical studies.
- TRULICITY is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

- **Counsel patients** regarding the potential risk for MTC and the symptoms of thyroid tumors (*e.g., a mass in the neck, dysphagia, dyspnea, or persistent hoarseness*).
- **Instruct patients** to contact their healthcare provider (HCP) promptly if these symptoms occur.
- **Refer patients** to an endocrinologist for further evaluation if thyroid nodules are noted upon physical examination or neck imaging.
- Routine monitoring of serum calcitonin (a biomarker of MTC) or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with TRULICITY. 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. **Refer patients** to an endocrinologist for further evaluation if serum calcitonin is measured and found to be elevated.

Risk of Pancreatitis

- Pancreatitis has been reported with the use of glucagon-like peptide-1 (GLP-1) receptor agonists. Cases of pancreatitis have been described in association with TRULICITY during clinical trials.



- **Counsel patients** to contact their HCP promptly if they experience symptoms of pancreatitis (*e.g., persistent, severe abdominal pain sometimes radiating to the back, which may or may not be accompanied by vomiting*).
- **Immediately discontinue** TRULICITY if pancreatitis is suspected. Perform confirmatory tests, and initiate appropriate management. If pancreatitis is confirmed, TRULICITY should not be restarted.
- **Consider** other antidiabetic therapies for patients with a history of pancreatitis. TRULICITY has not been studied in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis.

Indication

TRULICITY (dulaglutide) is a GLP-1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

TRULICITY is not recommended as first-line therapy for patients with type 2 diabetes mellitus inadequately controlled on diet and exercise.

What is the TRULICITY 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 TRULICITY outweigh the potential risk of MTC and the risk of pancreatitis. This factsheet is required by the FDA as part of the TRULICITY REMS program.

Please visit www.TRULICITYREMS.com for further information.

Reporting Adverse Events

To report adverse events among patients taking TRULICITY, contact:

- Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) and/or
- FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please contact The Lilly Answers Center at 1-800-545-5979 with any questions about the information in this factsheet or the safe and effective use of TRULICITY.

This factsheet does not contain the complete safety information for TRULICITY. Please refer to the Prescribing Information, including Boxed Warning, for further information.


[Prescribing Information including Boxed Warning](#)
[Medication Guide](#)

Trulicity™ REMS (Risk Evaluation and Mitigation Strategy)

What is the Trulicity REMS?

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration to ensure that the benefits of the drug outweigh its risks.

The purpose of the Trulicity REMS is to inform healthcare providers (HCPs) about the following risks of Trulicity:

- Potential Risk of Medullary Thyroid Carcinoma
 - Thyroid C-cell tumors have been observed in rodent studies with glucagon-like peptide-1 (GLP-1) receptor agonists.
 - It is unknown whether Trulicity causes thyroid C-cell tumors, including medullary thyroid carcinoma in humans.
 - Counsel patients regarding the risk of MTC and the symptoms of thyroid tumors.
- Risk of Pancreatitis
 - Pancreatitis has been reported with the use of GLP-1 receptor agonists. Cases of pancreatitis have been described in association with Trulicity during clinical trials.
 - Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. Consider other anti-diabetic therapies in patients with a history of pancreatitis.

[A non-promotional fact sheet](#), reviewed by FDA, with more detailed safety information about these risks is available.

Materials for Healthcare Providers:

- » [Trulicity REMS Factsheet for Healthcare Providers](#)
- » [REMS Letters to Healthcare Providers](#)

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/s/

NAOMI B REDD
09/17/2014

CYNTHIA L LACIVITA
09/18/2014
Concur

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: September 11, 2014

Reviewers: Naomi Redd, PharmD, Risk Management Analyst
DRISK
Kate Heinrich Oswell, MA, Senior Health Communications Analyst, DRISK

Team Leader: Doris Auth, PharmD, Acting Team Leader
DRISK

Division Director: Cynthia LaCivita, PharmD, Acting Division Director,
DRISK

Subject: Review of the amended proposed REMS September 9, 2014

Drug Name(s): dulaglutide (Trulicity®)

Therapeutic Class: Glucagon-like peptide 1 (GLP-1) receptor agonist

Dosage and Route: 1.5mg/0.5ml, and 0.75mg/0.5ml subcutaneous

Application Type/Number: BLA 125469

Applicant/sponsor: Eli Lilly and Company

OSE RCM #: 2013-2184

***** This document contains proprietary and confidential information that should not be released to the public. *****

1 INTRODUCTION

This review provides comments on the amended proposed risk evaluation and mitigation strategy (REMS) for dulaglutide submitted on September 9, 2014. Eli Lilly is seeking approval for dulaglutide as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). Revisions to Eli Lilly's amended REMS are based on labeling negotiations completed on August 22, 2014.

As in alignment with other drugs in the glucagon-like peptide-1 (GLP-1) receptor agonists class, in addition to the wide prescriber population likely to prescribe and dispense dulaglutide, DRISK has determined that a communication plan (CP) REMS for dulaglutide is necessary to ensure the benefits of dulaglutide outweigh the risk of pancreatitis and potential risk of medullary thyroid carcinoma (MTC).

2 MATERIALS REVIEWED

- Eli Lilly's proposed amended CP REMS submitted September 9, 2014
- Draft of label August 22, 2014

Previous DRISK reviews related to the original submission

- May 30, 2014 – DRISK REMS Review for Dulaglutide BLA 125469; Redd N.
- August 25, 2014 – DRISK REMS Review for Dulaglutide BLA 125469; Redd N.

3 RESULTS OF REVIEW

The Sponsor accepted the revisions received from the Agency on August 27, 2014. Clarification regarding the risk of pancreatitis was updated to align with labeling to include (b) (4) pancreatitis to the REMS and all related communication plan materials. Addition of the lower strength of 0.75mg/0.5ml was also added to the logos on all related communication plan materials. The REMS Factsheet is three pages, and therefore must be edited to fit on two pages. The clinical review team is still undergoing labeling negotiations at this time to section 14. Revisions to this section is not expected to impact the content of the REMS, however, the REMS cannot be finalized until labeling is complete.

4 CONCLUSION AND RECOMMENDATIONS

DRISK finds the REMS acceptable provided that the necessary revisions identified in this review are made to the REMS Factsheet for this submission.

5 COMMENTS FOR THE SPONSOR

We acknowledge your submission of the proposed REMS for dulaglutide received on September 9, 2014. Note the minor edits made in the REMS document and REMS Supporting Document. In addition, the REMS Factsheet must be a one page document with information on the front and back. The current Factsheet exceeds these specifications. Remove the page number headers from the factsheet as this header would not appear on the final version that would be distributed as part of the REMS. If necessary, also edit the margins and/or decrease the size of the logo on the Factsheet to

ensure that all of the information can fit on two pages. Please review and make the indicated changes and resubmit the REMS, REMS materials, and REMS Supporting Document. Provide versions of all documents in Word, and include both clean and track changes versions. The REMS has not completed clearance within the Agency, and we remind you that the REMS and all of the communication plan materials must align with final labeling.

ATTACHMENTS

REMS Document

REMS Supporting Document

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/s/

NAOMI B REDD
09/11/2014

CYNTHIA L LACIVITA
09/12/2014
Concur

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: August 25, 2014

Reviewer: Naomi Redd, PharmD, Risk Management Analyst
DRISK

Team Leader: Doris Auth, PharmD, Acting Team Leader
DRISK

Division Director: Cynthia LaCivita, PharmD, Acting Division Director,
DRISK

Subject: Review of the amended proposed REMS June 30, 2014

Drug Name(s): dulaglutide (Trulicity®)

Therapeutic Class: Glucagon-like peptide 1 (GLP-1) receptor agonist

Dosage and Route: 1.5mg/0.5ml, and 0.75mg/0.5ml subcutaneous

Application Type/Number: BLA 125469

Applicant/sponsor: Eli Lilly and Company

OSE RCM #: 2013-2184

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1 INTRODUCTION

This review provides comments on the amended proposed risk evaluation and mitigation strategy (REMS) for dulaglutide submitted on June 30th, 2014. Eli Lilly is seeking approval for dulaglutide as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). Revisions to Eli Lilly's amended REMS are based on labeling negotiations completed on August 13th, 2014.

As in alignment with other drugs in the glucagon-like peptide-1 (GLP-1) receptor agonists class, in addition to the wide prescriber population likely to prescribe and dispense dulaglutide, DRISK has determined that a communication plan (CP) REMS for dulaglutide is necessary to ensure the benefits of dulaglutide outweigh the risk of pancreatitis and potential risk of medullary thyroid carcinoma (MTC).

2 MATERIALS REVIEWED

- Eli Lilly's proposed amended CP REMS submitted June 30th, 2014
- Draft of label August 13th, 2014

Previous DRISK review related to the original submission

- May 30th, 2014 – DRISK REMS Review for Dulaglutide BLA 125469; Redd N.

3 RESULTS OF REVIEW

The sponsor accepted the majority of revisions received from the Agency on May 30th, 2014. Final comments regarding the wording of the risks for pancreatitis as well as update to adding the strength of the lower dose of dulaglutide were added as revisions to the REMS and REMS materials received on June 30th, 2014. These updates were based on labeling negotiations completed on August 13th, 2014. Recommendations from the Office of Prescription Drug Promotion (OPDP) received on August 25, 2014 were to update language in the REMS materials based on revisions to the label on August 22nd, 2014. Other recommendations were to include the full indication of use for dulaglutide, including all of the limitations of use for dulaglutide. The purpose of the REMS materials is to provide succinct information on the indication (as outlined in the label), with the prescribing materials and medication guide attached as documents that provide the entire labeling information for dulaglutide. Therefore, DRISK has decided to keep the materials as outlined, with updated language from labeling revisions done on August 22nd, 2014.

4 CONCLUSION AND RECOMMENDATIONS

DRISK finds the REMS acceptable provided that the necessary revisions identified in this review are made to the REMS and REMS materials for this submission.

5 COMMENTS FOR THE SPONSOR

We acknowledge your submission of the proposed REMS for dulaglutide received on June 30, 2014 and have the following necessary revisions and comments:

1. REMS Document:

- a) Update the placeholder for the month and year that the REMS document will be approved.
 - b) Remove (b) (4) when discussing the risk of pancreatitis.
2. REMS Supporting Document:
 - a) Update all of the language and attachments for the REMS materials with final approved labeling.
3. REMS Letters:
 - a) Remove (b) (4) when discussing the risk on pancreatitis.
 - b) Add this language for pancreatitis so that it may align with labeling: “Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. Consider other anti-diabetic therapies in patients with a history of pancreatitis.”
 - c) Add this language for medullary thyroid carcinoma so that it may align with labeling: “Counsel patients regarding the risk of medullary thyroid carcinoma and the symptoms of thyroid tumors.”
 - d) Add the 0.75mg/0.5ml strength to all the logos.
4. REMS Factsheet:
 - a) Remove (b) (4) when discussing the risk on pancreatitis.
 - b) Add this language for pancreatitis: “TRULICITY has not been studied in patients with a history of pancreatitis to determine whether these patients are at increased risk for acute pancreatitis.”
 - c) Add the 0.75mg/0.5ml strength to the logos
5. REMS Website
 - a) Make the language discussing the risk of pancreatitis consistent with labeling and all other REMS materials.
 - b) Add the 0.75mg/0.5ml strength to the logo.

Provide versions of all documents in Word, and include both clean and track changes versions within 3 business days. We remind you that language in all REMS materials must reflect the approved final labeling, and that the REMS materials are not appropriate for use in a promotional manner. The REMS has not completed clearance within the Agency, and additional changes may be necessary.

ATTACHMENTS

1. Revised REMS Document
2. REMS Letters
 - REMS Letter for HCP (print version)
 - REMS Letter for HCP (email version)
 - REMS Letter for Professional Societies (print version)
 - REMS Letter for Professional Societies (email version)
3. REMS Factsheet
4. REMS Website
5. REMS Supporting Document

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/s/

NAOMI B REDD
08/25/2014

CYNTHIA L LACIVITA
08/25/2014
Concur

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: May 30, 2014

Reviewer(s): Naomi Redd, PharmD, Risk Management Analyst
DRISK
Kate Heinrich Oswell, Senior Health Communications Analyst, DRISK

Team Leader: Cynthia LaCivita, PharmD, Team Leader
DRISK

Division Director: Claudia Manzo, PharmD, Division Director, DRISK

Subject: Review of the sponsor's proposed communication plan
REMS

Drug Name(s): dulaglutide (Trulicity®)

Therapeutic Class: Glucagon-like peptide 1 (GLP-1) receptor agonist

Dosage and Route: 1.5mg/0.5ml, subcutaneous

Application Type/Number: BLA 125469

Submission Number: Original submission/Seq. No. 0000 (1)

Applicant/sponsor: Eli Lilly and Company

OSE RCM #: 2013-2184

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EXECUTIVE SUMMARY

This review documents DRISK's evaluation of the need for a risk evaluation and mitigation strategy (REMS) for dulaglutide. Eli Lilly and Company is seeking approval for dulaglutide as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). The Agency's review of this BLA is ongoing; therefore this initial review of the risk mitigation required could be amended depending on the results of the clinical safety review. Dulaglutide is a long acting GLP-1 receptor agonist, with a proposed indication as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

Byetta (exenatide), Bydureon (exenatide extended-release), Victoza (liraglutide), and Tanzeum (albiglutide) are currently FDA approved GLP-1 receptor agonists that are labeled for pancreatitis based on post marketing and clinical trial data. Labeling for the risk of medullary thyroid carcinoma (MTC) was based on nonclinical data of thyroid C-cell tumors at dose dependent and clinically relevant exposures with Victoza, Bydureon, and Tanzeum, and is reported in the label as a Boxed Warning. FDA required the implementation of REMS for all currently approved GLP-1 receptor agonists to address the risk for pancreatitis (Byetta, Bydureon, Victoza, and Tanzeum), the potential risk for thyroid C-cell tumors (Bydureon, Victoza, and Tanzeum), and the potential risk of renal failure (Byetta).

The efficacy of dulaglutide is based on five Phase 3 studies ranging from 52 to 104 weeks of controlled duration as monotherapy and as add-on to multiple oral anti-hyperglycemic medications and insulin. A total of 2,837 patients with T2DM received dulaglutide treatment in these trials. Dulaglutide demonstrated superior efficacy at the primary and final study endpoints (measured by change in HgbA1C) to placebo and each active comparator evaluated.

Gastrointestinal side effects were the most common adverse events reported with dulaglutide, with nausea and vomiting as the most commonly reported events leading to drug discontinuation or study withdrawal. Five patients developed pancreatitis in the dulaglutide arms, and there were 3 patients that developed pancreatic cancer. One patient was diagnosed with medullary thyroid carcinoma (MTC) in the clinical trial program.

The applicant submitted a REMS to address the risks of pancreatitis and MTC. The proposed REMS includes a communication plan (CP) consisting of letters to healthcare providers (HCPs) and a website.

Dulaglutide shares these same risks as the other long acting drugs in this class. Therefore, requiring a CP REMS for dulaglutide is necessary and consistent with the management of the risks of pancreatitis and thyroid C-cell tumors associated dulaglutide.

1 INTRODUCTION

This review documents DRISK's evaluation of the need for a risk evaluation and mitigation strategy (REMS) for dulaglutide. Eli Lilly and Company is seeking approval for dulaglutide as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

Because the Agency's review of this BLA is ongoing, this initial review of the risk mitigation required could be amended, depending on the results of the ongoing review. DRISK will reassess the need for additional risk management measures once FDA reviewers complete their assessment of the risks associated with dulaglutide.

1.1 BACKGROUND

Diabetes is a growing epidemic chronic health care issue. In the United States, nearly 26 million children and adults (8.3% of the population) have diabetes.¹ This includes the undiagnosed population, comprising of 7 million people. In adults, T2DM accounts for approximately 90-95% of all diagnosed cases.¹ It is estimated that the number of people with diagnosed and undiagnosed diabetes would increase to more than 44 million people by 2034.² The pathogenesis of diabetes is multifactorial, commonly involving insulin resistance, increased hepatic gluconeogenesis, and progressive loss of pancreatic beta cell function.² Cardiovascular disease, hypertension, blindness, and amputations are some of the complications resulting from poorly managed diabetes. Despite several medications available to treat T2DM and an overall greater emphasis on diabetes care, from 2007-2010 only 53% of adults with T2DM in the US achieved glycosylated hemoglobin (HgbA1C) below the recommended 7% target level by the American Diabetes Association.³ Less than 20% of people with diabetes achieved reduction in all 3 goals, which also included optimal blood pressure control of <130/80 mmHg and LDL <100mg/dL. Substantial opportunity exists to further improve diabetes control and reduce diabetes related morbidity and mortality.³

Dulaglutide. Dulaglutide is a long acting GLP-1 receptor agonist, with a proposed indication as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The GLP-1 receptor agonists are designed to mimic the effect of an endogenous incretin hormone, GLP-1, by stimulating pancreatic insulin secretion in a glucose-dependent fashion by suppressing pancreatic glucagon output, slowing gastric emptying time, and decreasing appetite.⁴ Dulaglutide is supplied as a solution in a prefilled syringe for subcutaneous injection 1.5mg/0.5ml to be taken once weekly.

¹ <http://www.cdc.gov/diabetes/pubs/factsheet11.htm?loc=diabetes-statistics> accessed May 6, 2014

² Campbell R et al. Clarifying the role of incretin-based therapies in the treatment of type 2 diabetes mellitus. *Clin Ther*; 2011 33 (5): 511-527.

³ Casagrande S et al. The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988-2010. *Diabetes Care*. 2013;36(8):2271-2279.

⁴ Dulaglutide Clinical Overview, section 2.5

*GLP-1 Receptor Agonists Safety Concerns.*⁵ Byetta (exenatide), Bydureon (exenatide extended-release), Victoza (liraglutide), and Tanzeum (albiglutide) are currently approved GLP-1 receptor agonists that are labeled for pancreatitis based on post marketing and clinical trial data. Labeling for the risk of medullary thyroid carcinoma (MTC) was based on nonclinical data of thyroid C-cell tumors at dose dependent and clinically relevant exposures with Victoza, Bydureon, and Tanzeum, and is reported in the label as a Boxed Warning. FDA required the implementation of REMS for all currently approved GLP-1 receptor agonists to address the risk for pancreatitis (Byetta, Bydureon, Victoza, and Tanzeum), the potential risk for thyroid C-cell tumors (Bydureon, Victoza, and Tanzeum), and the potential risk of renal failure (Byetta).

1.2 REGULATORY HISTORY

The following is the regulatory history and milestone meetings for dulaglutide:

- May 2, 2013 – PreBLA meeting for dulaglutide
- September 18, 2013 – BLA submitted
- February 13, 2014 – Mid-cycle meeting
- March 3, 2014 – Mid-cycle teleconference to the sponsor. The important issues relayed were from clinical and statistics in regards to the dose to market, CMC, and CDRH.
- September 18, 2014 – PDUFA Date

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Dulaglutide Clinical Overview, submitted September 17, 2013
- Dulaglutide Summary of Clinical Safety and Efficacy, submitted September 17, 2013
- Dulaglutide proposed REMS and REMS supporting document, submitted September 17, 2013
- Midcycle Communication slides, February 13, 2014
-  (b) (4)
- Dr. Joyce Weaver review of proposed REMS for albiglutide, BLA 125431, October 16, 2013
- Tanzeum approved REMS, April 15, 2014

3 OVERVIEW OF THE CLINICAL DEVELOPMENT PROGRAM

The Agency's review of the dossier submitted by the applicant for this BLA in support of the efficacy and safety is still ongoing at the time of this writing. Sections 3.1 and 3.2 below provide a high level summary of the information submitted to the Agency and the applicant's interpretation of these data.

⁵ Byetta, Bydureon, Victoza, and Tanzeum product labels.

3.1 EFFICACY⁴

The efficacy of dulaglutide is based on five Phase 3 studies ranging from 52 to 104 weeks of controlled duration as monotherapy and as add-on to oral anti-hyperglycemic medications (metformin and sitagliptin), exenatide twice daily, and insulin (lispro and glargine). A total of 2,837 patients with T2DM received dulaglutide treatment in these trials. Dulaglutide demonstrated efficacy at the primary and final study time points (measured by change in HgbA1C) to placebo and each active comparator evaluated.

3.2 SAFETY⁴

The safety database for dulaglutide contains 6,005 patients included in the Phase 2 and Phase 3 studies, of which 4,006 patients received at least 1 dose of dulaglutide. Gastrointestinal adverse events were the most common adverse events reported with dulaglutide which included nausea (16.8%), diarrhea (10.7%), and vomiting (9.3%). Nausea and vomiting were the most commonly reported events leading to drug discontinuation or study withdrawal at 1.1% and 0.5% respectively.

The adverse events outlined below have been identified by the applicant as potential risks of dulaglutide.⁶

Pancreatitis: A total of 151 patients had events that underwent pancreatic adjudication in Phase 2 and 3 studies. Nine of these patients (5 in dulaglutide, 1 in placebo, 3 in sitagliptin) were determined to have pancreatitis. In the 5 patients that experienced pancreatitis in the dulaglutide arms, 2 of them were classified as acute pancreatitis, 2, chronic, and 1 case of “unknown type.”

Effects on Thyroid C-Cells: One patient was diagnosed with medullary thyroid carcinoma (MTC) in the clinical trial program, and was classified as a serious event. The MTC was considered pre-existing based on 8-fold elevations in serum calcitonin at baseline. The patient underwent total thyroidectomy and recovered from the event. Evidence for the potential of thyroid C-Cell tumors from dulaglutide has been gleaned from nonclinical studies in rodents.

Hypersensitivity: The overall incidence of treatment-emergent dulaglutide anti-drug antibodies (ADA) in the Phase 2 and Phase 3 trials was 1.6% versus 0.7% in patients treated with placebo or non-GLP-1 comparators. Among the 64 patients with treatment-emergent dulaglutide ADA, 34 (0.9%) had dulaglutide neutralizing ADA.

Pancreatic Malignancy^{4,6}: Three patients in the clinical program developed pancreatic cancer. One patient was diagnosed within 1 week of his first and only dose of dulaglutide. The sponsor determined that the cancer was preexisting in this patient. The second patient was diagnosed 5 months after randomization to dulaglutide. Given the patient’s abbreviated time on dulaglutide, and assessment of the tumor (determined to be large, locally advanced, and unresectable), the sponsor has determined that this malignancy was also likely preexisting. Lastly, there was another pancreatic carcinoma case which resulted in death in which dulaglutide could not be ruled out.

⁶ Dulaglutide US Risk Management Plan

Deaths: Seventeen deaths occurred in the clinical trials; 9 of these deaths were in patients who received dulaglutide⁷. Three of the deaths were from pancreatic cancer as described above. The other deaths included: cerebrovascular accident (1), myocardial infarction (1), staphylococcal sepsis (1), cardiac failure (1), pneumonia (1), and 1 unclassified death.⁸

4 REMS FOR OTHER GLP-1 RECEPTOR AGONISTS

The safety profile of all currently FDA-approved GLP-1 receptor agonists (Byetta [exenatide], Bydureon [exenatide long acting], Victoza [liraglutide], and Tanzeum [albiglutide]) includes the risk for pancreatitis. Byetta has a potential risk of renal failure, sometimes requiring hemodialysis and renal transplantation. Due to their long acting mechanism of action, Victoza, Bydureon, and Tanzeum have the additional risk for thyroid C-cell tumor. Although the risk for thyroid C-cell tumors is supported at this time by non-clinical data, this risk is included as Boxed Warnings for Victoza, Bydureon, and Tanzeum. Due to the similarities in risks, A REMS with a communication plan (CP) was required by the Agency for all of the currently approved GLP-1 receptor agonists highlighting the risk of pancreatitis and potential risk for thyroid-C cell tumors. Byetta is the only GLP-1 agonist that is not associated with thyroid C-cell tumor, believed to be due to its shorter acting mechanism of action. Renal failure was the other risk in addition to pancreatitis that was outlined in the Byetta REMS. On August 5th, 2011 the REMS for Byetta was released after its first year assessment because the Agency determined at that time the REMS was meeting its goals.

The CP REMS for Byetta, Victoza, and Bydureon consisted of Dear Healthcare Professional (DHCP) letters and a REMS website. The REMS for Victoza and Bydureon also included Highlighted Information for Prescribers. Tanzeum is the first drug in this class to be approved with a REMS CP plan that includes REMS communications (brief, risk message-focused letters for HCPs and professional societies), a REMS Factsheet, and a REMS website. These CP tools are revised versions of tools previously employed in other REMS for GLP-1 receptor agonists which are based on the experience gained from the assessments of other REMS. The revised versions of the tools was done to make information available in a succinct and easy to read, risk message-focused format.

5 RATIONALE FOR A REMS

Dulaglutide shares these same risks as the other long acting drugs in this class. Therefore, requiring a CP REMS for dulaglutide is necessary and consistent with the management of the risks of pancreatitis and potential risk of thyroid C-cell tumors associated dulaglutide.

Key dulaglutide CP REMS messages must be consistent with the product labeling and may include the following: 1) dulaglutide's associated risk of acute pancreatitis; 2) HCPs consideration of other antidiabetic therapies in patients with a history of pancreatitis, gallstones, alcoholism, high blood triglycerides, and the use of concomitant medications that may potentiate pancreatitis; 3) patients should be monitored for signs and symptoms of pancreatitis when treated with dulaglutide; 4) if pancreatitis is suspected, dulaglutide

⁷ Dulaglutide Summary of Clinical Safety Section 2.7.4

⁸ Section 5.3.5.3 Significant and Notable Patients

should be discontinued; 5) if pancreatitis is confirmed, dulaglutide should be discontinued and not be restarted; and 6) patients must be counseled to be aware of the signs and symptoms of acute pancreatitis (i.e., severe and persistent abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting) and the importance of reporting these symptoms to their HCPs as soon as possible; 7) dulaglutide is potentially associated with the risk of MTC and thyroid C cell tumors; 8) HCPs must consider other anti-diabetic therapies in patients with a personal or family history of MTC, and in patients with Multiple Endocrine Neoplasia Syndrome type 2 (MEN 2).

Since HCPs are the target of the REMS messages, DRISK determined that although it is important to include a Medication Guide (MG) as part of dulaglutide's label, its inclusion as part of the REMS is not necessary. In addition, DRISK determined that a REMS with elements to assure safe use (ETASU) is not required to maintain the risk: benefit balance of dulaglutide.

6 REMS PROPOSED BY THE SPONSOR AND DRISK'S COMMENTS

The applicant submitted a proposed REMS comprising a CP.

6.1 GOALS

The applicant proposed the following goal for the REMS:

- To inform healthcare providers (HCPs) about the potential risk of (b) (4) pancreatitis and the potential risk of medullary thyroid carcinoma associated with the use of TRADENAME.

Reviewer comment: We propose the following goal statement –

The goal of the TRADENAME REMS is to mitigate the risk of (b) (4) pancreatitis and the potential risk of medullary thyroid carcinoma associated with the use of TRADENAME by:

- *Informing healthcare providers (HCPs) about the risk of (b) (4) pancreatitis associated with TRADENAME.*
- *Informing HCPs about the potential risk of medullary thyroid carcinoma associated with TRADENAME.*

The rationale for the modification of the REMS goal is to make a distinction between the overarching goal of the REMS, and its related measurable objective, which is the focus of the REMS assessment process.

6.2 REMS ELEMENTS

Communication Plan: The applicant proposed the following language for implementation of a CP:

Eli Lilly and Company (Lilly) will implement a Dear Healthcare Professional (DHCP) letter and REMS-specific website as a communication plan to HCPs likely to prescribe

TRADENAME. A DHCP letter will be mailed within 60 days of product approval or at the time of product launch, whichever is sooner, and again after 12 months. The DHCP letter will contain the FDA-approved labeling. This communication will emphasize the potential risk of (b) (4) pancreatitis and the potential risk of medullary thyroid carcinoma.

Lilly will ensure that all materials listed in or appended to the TRADENAME REMS program will be available through the TRADENAME REMS program website. This information will be available on the website from the date of approval until the release of REMS requirement.

Reviewer comment: The CP proposed by Lilly will require revisions. The REMS materials should be expanded to include REMS communications (i.e., concise risk message-focused letters for HCPs and professional societies), a REMS Factsheet, and a REMS website. These CP tools are revised versions of tools previously employed in other REMS for GLP-1 receptor agonists and aligns with the materials in the recent approval of Tanzeum REMS. The revisions are based on the experience gained from the assessments of other REMS and feedback from FDA's Health Professional Organization Conference in October 2012. The change to the tools were made to provide a concise risk message and to improve the format for electronic letters in an attempt to making this information more accessible to HCPs, which in turn will increase the probability that prescribers will be able to receive and view risks messages associated with dulaglutide. An increase in awareness of the REMS materials may result in improvements in prescribers' knowledge of the risks associated with dulaglutide. Comments to sponsor regarding the necessary revisions are in section 8 of this review.

Timetable for Submission of REMS Assessments: The applicant proposed to submit REMS Assessments to the FDA at 18 months, 3 years, and 7 years from the date of the initial approval of the REMS.

Reviewer Comment – DRISK finds this timetable for submission acceptable.

6.3 REMS ASSESSMENT PLAN

The proposed REMS assessment plan includes methodologies to assess healthcare provider awareness of the following:

- the appropriate patient population characteristics
- the potential risk for (b) (4) pancreatitis and the need for prompt evaluation of patients who develop symptoms suggestive of pancreatitis
- the potential risk for MTC
- the need for assessment of identification and treatment of MTC and (b) (4) pancreatitis after initiation of dulaglutide

The 18-month REMS assessment will also report the number of e-mail and fax transmissions that were attempted and unsuccessful, as well as the number that were sent via first class mail.

Reviewer comment – DRISK recommends that the dulaglutide REMS assessment report must be expanded. See section 8 in the assessment plan.

7 CONCLUSION AND RECOMMENDATIONS

As in alignment with other drugs in the GLP-1 receptor agonists class, in addition to the wide prescriber population likely to prescribe and dispense dulaglutide, DRISK has determined that a CP REMS for dulaglutide is necessary to ensure the benefits of dulaglutide outweigh the risk of pancreatitis and potential risk of MTC.

At this time in the review process for this application, MTC and pancreatitis have been identified as the only risks to be included in this REMS. Evidence to support inclusion of other serious risks in the REMS may surface during the BLA review process. DRISK will reassess the need for revisions to the risk management measures once FDA reviewers complete their analysis of efficacy and safety with dulaglutide.

The REMS document proposed by the applicant has been revised by DRISK, and recommends the Division of Metabolism and Endocrinology Products send the applicant the comments included in section 8 below.

8 COMMENTS FOR THE SPONSOR

We acknowledge your submission of the proposed REMS for dulaglutide received on September 17, 2013 and have the following necessary revisions and comments:

1. At this point in the BLA review process, MTC and pancreatitis are the only risks to be included in this REMS; evidence to support inclusion of other serious risks in the REMS may surface during the remaining BLA review process.
2. Goal statement: the goal statement was restated for clarity as follows:

The goal of the TRADENAME REMS is to mitigate the risk of (b) (4) pancreatitis and the potential risk of medullary thyroid carcinoma associated with the use of TRADENAME by:

- Informing healthcare providers (HCPs) about the risk of (b) (4) pancreatitis associated with TRADENAME.
- Informing HCPs about the potential risk of medullary thyroid carcinoma associated with TRADENAME.

The rationale for the modification of the REMS goal is to make a distinction between the overarching goal of the REMS, and its related measurable objectives, which is the focus of the REMS assessment process.

3. Key dulaglutide CP REMS messages must be consistent with the product's final labeling and may include the following, as applicable:
 - Dulaglutide is associated with the risk of (b) (4) pancreatitis.
 - Dulaglutide is potentially associated with the risk of MTC.

- HCPs must consider other anti-diabetic therapies in patients with a personal or family history of MTC, and in patients with Multiple Endocrine Neoplasia Syndrome type 2 (MEN 2).
 - Patients should be monitored for signs and symptoms of pancreatitis when treated with dulaglutide.
 - If pancreatitis is suspected, dulaglutide should be discontinued.
 - If pancreatitis is confirmed, dulaglutide should be discontinued and not restarted.
 - Patients must be counseled to be aware of the signs and symptoms of (b) (4) pancreatitis (i.e., severe and persistent abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting), and the signs and symptoms of MTC, and the importance of reporting these to their physicians as soon as possible.
4. REMS document – a revised version of the REMS document is attached.
5. Communication Plan – the REMS should include the following communication tools: REMS letters, REMS Factsheet, and a REMS website.
- a) **REMS Letter** - replace the use of a standard Dear Healthcare Provider (DHCP) letter with concise, risk-focused REMS letters addressed to HCPs and relevant Professional Societies. FDA proposes having the REMS letters formatted in two different ways: print and electronic versions. The electronic version of the REMS letters should be email and handheld device-friendly. The objective of these changes is to improve the communication of the risk message among the growing HCP population of hand-held device users. The subject of the emails should be “Risk of Medullary Thyroid Carcinoma and (b) (4) Pancreatitis with TRADENAME (dulaglutide).” The outside of the mailed envelopes should state: "FDA Required REMS Safety Information: it should be printed in red, bolded, and a minimum size 14 font. It may be on two lines and should be boxed, for example:

**FDA Required REMS
Safety Information**

See proposed print and electronic REMS letter templates attached.

- b) **REMS Factsheet for Healthcare Providers**
 Create a REMS Factsheet for HCPs. This REMS Factsheet must be in a user-friendly format, including coloring, and any logos from TRADENAME REMS program; include bullets, boxes, and bold text to highlight important information; should have plenty of white space and a font size of at least 12; be printed on thicker card stock paper; be only one sheet with information on both sides of paper and heading should read: FDA Required TRADENAME REMS Safety Information.

See proposed Factsheet template attached.

c) **REMS Website**

Ensure the REMS website, is independent of link to the promotional and/or commercial website and non-REMS materials about the product. Do not include a link from the REMS website back to the www.TRADENAME.com website. The REMS website should also be accessible directly through a search engine. The REMS website will be available for the duration of the REMS.

We have made content edits to your website in a separate template, along with formatting suggestions. See proposed REMS website template attached.

6. Timetable for submission of REMS assessments – we are in agreement with the timetable for assessments that you have proposed.
7. REMS assessment plan: the dulaglutide REMS assessment report must include but not be limited to the following items:
 1. REMS communication plan activities:
 - a. Number of HCPs and professional societies targeted by the REMS.
 - b. Number of REMS letters sent to HCPs and professional societies via email, standard mail, and facsimile, and the dates the letters were sent. Include the number of letters sent via standard mail because the HCP did not have an email address, and the number sent because the email was undeliverable. For letters sent via email, include the number of letters successfully delivered, and the number of email letters opened by the recipients.
 - c. Number of REMS Factsheets distributed to HCPs during the 12 months after product launch.
 - d. Date when REMS website went live and number of total and unique site visits during the assessment period.
 2. Evaluation of HCPs' understanding of:
 - a. The potential risk of MTC
 - b. The risk of pancreatitis
 - c. The need for prompt evaluation of patients who develop symptoms suggestive of pancreatitis
 - d. Identification and treatment of ^{(b) (4)} pancreatitis after initiation of dulaglutide
 - e. Appropriate dulaglutide patient population characteristics

3. Safety surveillance
 - a. Dulaglutide utilization information including, but not limited to, indication and type of HCP (i.e., endocrinologist, general practitioner, internist, etc.)
 - b. Evaluation and post-marketing case reports of pancreatitis
 - c. Evaluation and post-marketing case reports of MTC
 - d. Any other relevant data and analysis employed to assess if the dulaglutide REMS is meeting its goals
 - e. The evaluation shall include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or elements should be modified. If a REMS modification is needed, provide an overview of the impact of the REMS modification on stakeholders and any additional evaluations needed as part of the REMS assessment plan to assess the impact of the proposed REMS modification.

The inclusion of REMS assessment report synopsis or executive summary, although not necessary is helpful in the Agency's review of the REMS Assessment Reports.

8. Education or communication provided as part of a REMS should emphasize the safety messages important for the safe use of the product.
9. Product marketing materials generally are not appropriate to educate about product risks.
10. Submit all planned materials (e.g., proposed communications, education materials, and REMS website) identified within the plan that will be necessary to implement your proposal.
11. We recommend pre-testing all REMS materials.
12. Update the REMS Supporting Document to reflect all the changes to the REMS, REMS appended materials, and REMS assessment plan.
13. HCP survey: Submit for review the detailed plan you propose to use to evaluate prescribers' understanding about the safe use of dulaglutide. You may submit the proposed plan after approval of the REMS; however submit it at least 90 days before you conduct the evaluation. Code the submission "REMS Correspondence." If the plan is to conduct the required assessment using a survey, make sure the submission includes all methodology and instruments used to evaluate the knowledge about the risks associated with and safe use of dulaglutide.
 - a) Recruit respondents using a multi-modal approach.
 - b) Explain how often you perform non-respondent follow-up reminders. If you use an incentive or honorarium, provide details on what is offered and

the estimated dollar value. Explain how you select recruitment sites. Submit for review any recruitment advertisements.

- c) Describe the rationale for your sample size. Report the 95% confidence interval around the expected level(s) of prescriber knowledge for each key risk(s).
- d) Define the expected number of prescribers to be contacted to obtain the proposed sample size, and how the sample is determined (selection criteria).
- e) Ensure the sample is demographically representative of the prescriber population regardless of the condition for which they prescribe it.
- f) When possible and appropriate, ensure the sample is diverse in terms of age, race, ethnicity, sex, and geographically.
- g) List the inclusion criteria for prescribers.
- h) Submit any screener instruments, and describe any quotas of sub-populations used.
- i) Explain how you administer surveys and the intended frequency. Offer respondents multiple options for completing the survey. Explain how you train surveyors.
- j) Explain how you control for limitations or bias associated with the methodology and survey instruments(s).
- k) Submit for review the introductory text used to inform respondents about the purpose of the survey. Tell potential respondents that their answers will not affect their ability to prescribe dulaglutide, and that their answers and personal information will be kept confidential and anonymous. All text, including questions and answers, are to be non-promotional in language and tone.
- l) Clarify in your methodology that respondents are eligible for one wave of the survey only.
- m) Analyze results on an item-by-item or variable-by-variable basis. You may present the data using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables). You may stratify the data by any relevant variable, and also in aggregate. Submit all methodology and instruments utilized with your assessments.
- n) The assessment evaluates how effective the REMS is in achieving the goal(s) by evaluating HCPs' knowledge of the risks and safe use associated with dulaglutide. The assessment does not assess HCPs' comprehension of the educational materials. Do not offer respondents an opportunity to read or see any educational materials (e.g., prescribing

information, communications, promotional materials, websites, videos, etc.) again prior to taking the survey.

- o) Submit for review the survey instruments (e.g., questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in any educational materials.
- p) Ensure the HCP knowledge survey includes a section with questions asking about the specific risks and safety information conveyed in the educational materials. Ensure questions are not biased or leading and that multiple choice questions include an instruction to "select all that apply." Answer options should include an appropriate number of foils. Ensure each question has an "I don't know" answer option. Randomize the order of the multiple choice responses on each survey.
- q) Order the survey questions so the risk-specific questions are asked first, followed by questions about receipt of the educational materials. Collect demographic questions last or as part of any screener questions. Do not allow respondents the opportunity or ability to go back to previous questions in the survey. Explain if and when any education will be offered for incorrect responses.

ATTACHMENTS

- 1. Revised REMS Document
- 2. Sample of REMS Letters
 - REMS Letter for HCP (print version)
 - REMS Letter for HCP (email version)
 - REMS Letter for Professional Societies (print version)
 - REMS Letter for Professional Societies (email version)
- 3. Sample of REMS Website

17 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NAOMI B REDD
05/30/2014

CLAUDIA B MANZO
05/30/2014
concur