CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022200Orig1s000

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:	022200
Products:	BYDUREON (exenatide extended-release for injectable suspension), 2 mg
APPLICANT:	Amylin Pharmaceuticals, Inc.
FROM:	Mary H. Parks, M.D.
DATE:	January 8, 2012

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 BYDUREON (exenatide extended-release for injectable suspension) to ensure that the benefits of the drug outweigh the potential serious risk of medullary thyroid carcinoma identified in non-clinical studies, and a signal of a serious risk of acute pancreatitis, including hemorrhagic and necrotizing pancreatitis, identified in postmarketing reports for the currently approved formulation of exenatide injection, BYETTA®. In reaching this determination, we considered the following:

A. Approximately 24 million people in the United States have type 2 diabetes mellitus, of whom more than one-third will require more than one anti-diabetic agent to maintain adequate glycemic control within several years of initiation of drug therapy. In 2008, approximately (b) (4) patients filled a prescription for the currently approved formulation of exenatide injection, BYETTA®.

B. Patients with type 2 diabetes mellitus who require anti-diabetic medication for glycemic control are at risk for a variety of complications including heart disease, stroke, blindness, kidney failure, nervous system damage, amputations, and death if untreated.

C. BYDUREON (exenatide extended-release for injectable suspension) has been shown to achieve a mean reduction from baseline in hemoglobin A1c over 30 weeks of approximately 1.9%. Some of the complications listed above can be prevented or delayed with good glycemic control. BYDUREON (exenatide extended-release for injectable suspension) 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 acute pancreatitis, including hemorrhagic and necrotizing pancreatitis, BYDUREON (exenatide extended-release for injectable suspension) is associated with the following other adverse effects, including gastrointestinal adverse events such as nausea and diarrhea, serious hypoglycemia especially when used with an insulin secretagogue (e.g., a sulfonylurea), hypersensitivity, renal failure, and injection site reactions.

F. BYDUREON (exenatide extended-release for injectable suspension) is not a new molecular entity.

The application for BYDUREON was initially submitted on May 4, 2009 and the applicant was notified on February 16, 2010 that a REMS would be required, should the application be approved. The applicant was notified that the REMS must include a Medication Guide, communication plan, and a timetable for submission of assessments of the REMS.

After consultations between OND and OSE, we have determined that the Medication Guide is no longer necessary to ensure the benefits of the drug outweigh the risks described above because the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208.1. The Medication Guide will be part of the approved labeling in accordance with 21 CFR 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA

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

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/s/

AMY G EGAN
01/25/2012

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

Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	December 23, 2011
Reviewer(s):	Joyce Weaver, Pharm.D., Division of Risk Management (DRISK) Anahita Tavakoli, M.A., Health Communications Analyst, DRISK
Team Leader:	Cynthia LaCivita, Pharm.D., DRISK
Division Director	Claudia Karwoski, Pharm.D., DRISK
Drug Name(s):	Bydureon, exenatide extended-release
Therapeutic Class:	Glucagon-like peptide-1 (GLP-1) receptor agonist
Dosage and Route:	2 mg subcutaneous injection once weekly
Application Type/Number:	022200
Submission Number:	DARRTS #s 43, 53; EDR serial #s 34, 51
Applicant/sponsor:	Amylin Pharmaceuticals, Inc
OSE RCM #:	2011-2836

CONTENTS

1 INTRODUCTION

This document reviews the REMS proposal for Bydureon, a once weekly formulation of exenatide injection.

1.1 BACKGROUND

Bydureon is an extended-release formulation of exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist. Bydureon is being considered for an indication to be used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Bydureon is not considered first-line therapy for patients inadequately controlled on diet and exercise, is not a substitute for insulin and should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

1.2 REGULATORY HISTORY

The following are regulatory milestones pertinent to the REMS for Bydureon:

- May 4, 2009—NDA 022200 submitted for Bydureon, extended release exenatide.
- February 16, 2010—The FDA sent a REMS Notification letter to the sponsor notifying of the need for a REMS comprising a Medication Guide (MG) + communication plan (CP) to ensure the benefits of Bydureon outweigh its risks of medullary thyroid carcinoma and acute pancreatitis, including necrotizing and hemorrhagic pancreatitis. The letter specified that the CP should include a Dear Healthcare Professional (DHCP) letter, a Direct Mail letter, a document with highlighted info for prescribers, and a website.
- March 12, 2010—a complete response (CR) action was taken citing product quality deficiencies and the need for REMS.
- April 22, 2010—the NDA was resubmitted; the resubmission included a REMS submission.
- September 21, 2010—DRISK reviewed the REMS submission, and prepared comments for the sponsor. The comments were sent to the sponsor September 28, 2010.
- October 18, 2010—A CR action was taken citing the need for QT data; the letter reiterated the need for a REMS.
- May 23, 2011—Responding to a question from the sponsor, the FDA advised the sponsor that it would be appropriate to remove MG from the REMS.

- July 28, 2011—The application was resubmitted; the resubmission included a REMS submission comprising a CP.

- December 7, 2011—Agency comments on the REMS were sent to the sponsor

- December 8, 2011—The sponsor resubmitted the REMS, incorporating Agency comments

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

REMS proposal in submission of July 28, 2011 and REMS amendment of December 8, 2011

2.2 ANALYSIS TECHNIQUES

The REMS submissions were reviewed for responsiveness to previous Agency comments regarding the Bydureon REMS.

3 RESULTS OF REVIEW OF PROPOSED BYDUREON RISK EVALUATION AND MITIGATION STRATEGY

3.1 OVERVIEW OF CLINICAL PROGRAM OR POSTMARKETING EXPOSURE

Bydureon was studied in two comparator-controlled studies, one a 30-week study and the other a 24-week study. Subjects (n=547 total in the two studies) with type 2 diabetes whose glycemic control was inadequate with diet and exercise alone or with oral antidiabetic therapy were studied. Subjects received either Bydureon 2 mg once weekly or Byetta (initially 5 mcg BID, then10 mcg BID after 4 weeks), in addition to existing oral antidiabetic agents. The primary endpoint was change in HbA_{1c} from baseline to the end of the study (or the last value at time of early discontinuation). The change in HbA_{1c} was greater for subjects treated with Bydureon.

3.2 SAFETY CONCERNS

The draft labeling for Bydureon includes a boxed warning for thyroid C-cell tumors. The *Warnings and Precautions* section of the labeling includes information about acute pancreatitis, hypoglycemia, use in patients with renal impairment, use in patients with gastrointestinal disease, immunogenicity, hypersensitivity, and the lack of data about macrovascular outcomes. Of the safety concerns in the *Warnings and Precautions* section of the labeling, the risks of thyroid C-cell tumors and acute pancreatitis require risk mitigation beyond labeling. This is consistent with the REMS required for Byetta, the immediate-release formulation of exenatide.

3.3 GOALS

The goal of the Bydureon REMS is to inform healthcare professionals about the risk of acute pancreatitis and the potential risk of medullary thyroid carcinoma associated with Bydureon.

3.4 REMS ELEMENTS

The REMS is comprised of a communication plan.

3.4.1 Medication Guide

The labeling includes a Medication Guide, but the REMS does not include the Medication Guide.

3.4.2 Communication Plan

The communication plan includes a Dear Healthcare Professional (DHCP) letter and Highlighted Information for Prescribers. The DHCP letter is to be sent within 60 days of approval or at product launch, and then again after 6 months. The letter will be available on the REMS website for 1 year after the date of approval. The targets of the letter are likely prescribers. The letter is to be sent by electronic mail when possible, and by mail or facsimile if the letter cannot be sent via electronic mail. The letter will be sent to prominent professional organizations that represent likely prescribers as well.

The Highlighted Information for Prescribers will be provided by the sponsor's representatives during the first discussion of Bydureon with all healthcare professionals detailed during the first 6 months after launch.

3.4.3 Elements to Assure Safe Use

The REMS does not include elements to assure safe use.

3.4.4 Implementation System

The REMS does not include an implementation system.

3.4.5 Timetable for Submission of Assessments

REMS assessments will be submitted at 1 year, 2 years, and in the 7th year following approval.

3.5 REMS ASSESSMENT PLAN

Using surveys of prescribers, Amylin will assess healthcare providers' understanding of the risks of pancreatitis and medullary thyroid carcinoma (MTC). The surveys will also be used to assess healthcare providers' identification and treatment of MTC and and acute pancreatitis in patients receiving Bydureon. The assessment reports will include data regarding the distribution of the communication materials, including the number of electronic mail pieces delivered and opened. Amylin will include data establishing the extent of use of Bydureon as first-line therapy.

4 DISCUSSION

The sponsor has responded to the comments and agreed to the requested changes to the REMS. We have several additional changes to the REMS and the REMS materials, including a change to add a REMS assessment in the 7th year.

5 CONCLUSION

The REMS for Bydureon (exenatide), extended-release suspension for injection, REMS submission dated December 8, 2011 contains the appropriate and agreed upon revisions on the communication plan REMS as requested by the Agency on December 7, 2011. The REMS Supporting Document outlines the information and content that the applicant will use to assess the effectiveness of the Bydureon REMS in achieving the goals.

Providing the sponsor makes the necessary revisions identified in the REMS and the REMS materials, the Bydureon REMS is acceptable to the Office of Surveillance and Epidemiology, the Division of Risk Management.

6 RECOMMENDATIONS

The OSE, DRISK recommends approval of the Bydureon REMS after the required changes are made. The amended documents showing the required changes are attached.

In addition, we recommend the text below be included in the approval letter.

- Submit a detailed document outlining the final methodology and content of the healthcare provider survey at least 90 days prior to initiating the conduct of the survey. Three healthcare provider surveys will be conducted in accordance with the REMS assessment report submission timeline: 1 year, 2 years, and in the 7th year.
- Submit a detailed document outlining the final methodology for conducting case review evaluations of pancreatitis at least 90 days prior to initiating the evaluation. Three evaluations will be conducted in accordance with the REMS assessment report submission timeline: 1 year, 2 years, and in the 7th year.

1. The 1-year, 2-year, and 7th-year REMS assessment reports will include the following:
   a) The results of surveys assessing healthcare providers' understanding of the critical content related to pancreatitis and medullary thyroid cancer. The assessment will include healthcare providers' awareness of appropriate BYDUREON patient population characteristics, the potential risk for medullary thyroid carcinoma, and the need for prompt evaluation of patients who develop symptoms suggestive of pancreatitis.
   b) The results of surveys assessing healthcare providers' identification and treatment of medullary thyroid carcinoma and acute pancreatitis after initiation of BYDUREON.
   c) The results of case series review of targeted safety surveillance of spontaneously reported cases to of acute pancreatitis.
   d) The percentage of targeted prescribers who are presented with the Highlighted Information for Prescribers via sales specialists or medical information department.
   e) An analysis of use data establishing the extent of first-line use of BYDUREON.

f) An evaluation of the extent to which the elements of the REMS are meeting the goals of the REMS and whether modifications to the elements or goals are needed.

2. The 1-year REMS assessment reports will include the number of letters sent via email, standard mail, and facsimile, and the dates the letters were sent. For the letters sent via email, include the number of letters sent via standard mail because the healthcare provider 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.

ATTACHMENTS

Bydureon REMS and REMS Supporting Document

NDA 022-200

Initial REMS approvaled mm/yyyy
BYDUREON™ (exenatide extended-release for injectable suspension)
A glucogon-like peptide-1 (GLP-1) receptor agonist

Amylin Pharmaceuticals, Inc.

Contact: Sean Zhao, M.D., Ph.D.
Vice President, Global Safety
9360 Towne Centre Drive
San Diego, CA 92121
Phone: 858-736-8999
Cell Phone: 858-349-5220
Fax: 858-625-0737
sean.zhao@amylin.com

858-552-2200

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

- To inform healthcare professionals about the risk of acute pancreatitis (including necrotizing and hemorrhagic pancreatitis) and the potential risk of medullary thyroid carcinoma associated with BYDUREON.

II. REMS ELEMENTS

A. Communication Plan

Amylin Pharmaceuticals will implement the following elements of a communication plan:

1. A Dear Healthcare Professional (DHCP) letter will be sent within 60 days of product approval or at the time of product launch, whichever is sooner, and again after 6 months. The letter will be available via a link from the BYDUREON website and through the medical information department for 1 year following approval of the REMS. The intended audience for this letter is Healthcare Professionals (HCPs) who are likely to prescribe BYDUREON.

The audience to receive the letter includes HCPs who have written at least one BYETTA prescription within the last 12 months, which includes physicians, nurse practitioners, and physicians' assistants predominantly in the specialties of endocrinology, internal medicine, and family practice. In addition, all endocrinology specialists and retail pharmacists will receive the letter. These data are obtained from IMS Health Xponent Plan Track Weekly™ and the~~our~~ Amylin Customer Master database. The list is comprised of prescribers who

have written BYETTA prescriptions within the past 12 months as well as all endocrinologists (prescribers and non-prescribers of BYETTA). Amylin will obtain electronic mail addresses for the targeted HCPs and send the DHCP letter via electronic mail. If a targeted HCP's email address is not available, or if an email is undeliverable, the HCP will receive the letter through the mail or via facsimile.

Within 60 days of product approval or at the time of product launch, whichever is sooner, and again after 6 months, Amylin will send the DHCP letter to the following professional organizations, and will request that the letter be provided to the members of the professional organizations: the American College of Physicians, the American Medical Association, the American Academy of Family Physicians, the American College of Osteopathic Family Physicians, the American College of Clinical Pharmacy, the American Pharmacists Association, the American Society of Health-System Pharmacists, the American Academy of Nurse Practitioners, the American Association of Clinical Endocrinologists, the Endocrine Society, the American Diabetes Association, the American Association of Diabetes Educators, the American Association of Physicians Assistants, the Association of Managed Care Pharmacy, the National Association of Managed Care Physicians.

The letter will be provided to MedWatch at the same time it is provided to the professional organizations.

The Dear Healthcare Professional letter is part of the REMS and is appended.

2. The Highlighted Information for Prescribers will be provided by Amylin representatives during the first discussion of BYDUREON with all HCPs detailed during the first 6 months after launch.

The Highlighted Information for Prescribers is part of the REMS and is appended.

All components of the communication plan will be updated to reflect any changes in labeling for the risks outlined above.

Amylin will make the REMS, the DHCP letter, the Medication Guide, the Highlighted Information for Prescribers, and professional labeling available via a REMS-specific link from the BYDUREON website as well as through the medical information department for one year after the initial date of approval. The Medication Guide, the Highlighted Information for Prescribers and professional labeling will also be available via hard copy from Amylin representatives and through Amylin's call center for one year after the initial date of approval.

The BYDUREON REMS website is part of the REMS, the landing page screen shot is appended.

C. Elements to Assure Safe Use

Elements to Assure Safe Use are not required.

D. Implementation System

An Implementation System is not required.

E. Timetable for Submission of Assessments

Amylin Pharmaceuticals, Inc. will submit REMS Assessments to FDA at 1 year, ~~and~~ 2 years, and in the 7th year 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. Amylin Pharmaceuticals, Inc. will submit each assessment so that it will be received by the FDA on or before the due date.

Appendix 1: Dear Healthcare Professional Letter

Month, 2011

IMPORTANT DRUG WARNING

Dear Healthcare Professional:

Amylin Pharmaceuticals, Inc. is writing to inform you of important safety information about BYDUREON™ (exenatide extended-release for injectable suspension), a once weekly GLP-1 receptor agonist for the treatment of type 2 diabetes. The U.S. Food and Drug Administration (FDA) has approved BYDUREON as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure that the benefits of BYDUREON outweigh the following potential risks including:

- Medullary Thyroid Carcinoma (MTC); and
- Acute Pancreatitis.

Because of these potential risks, BYDUREON is <u>not</u> recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.

WARNING: RISK OF THYROID C-CELL TUMORS

Exenatide extended-release caused an increased incidence in thyroid C-cell tumors at clinically relevant exposures in rats compared to controls. It is unknown whether exenatide extended-release causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be determined by clinical or nonclinical studies. BYDUREON is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with BYDUREON. Patients should be counseled regarding the risk and symptoms of thyroid tumors.

<u>Potential Risk of Medullary Thyroid Carcinoma (MTC)</u>

- Patients with thyroid nodules noted on physical examination or neck imaging should be referred to an endocrinologist for further evaluation.
- 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 BYDUREON. 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.

Risk of Acute Pancreatitis

- Based on postmarketing data exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis.
- After initiation of BYDUREON, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting).
- If pancreatitis is suspected, BYDUREON should promptly be discontinued, confirmatory tests should be performed, and appropriate management should be initiated.
- If pancreatitis is confirmed, BYDUREON should not be restarted.
- Consider other antidiabetic therapies in patients with a history of pancreatitis (b) (4)

Appropriate Patient Selection

BYDUREON:

- Is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- Is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.
- Has not been studied in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis while using BYDUREON. (b) (4) in patients with a history of pancreatitis.
- Should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
- Has not been studied in combination with insulin and concurrent use is not recommended.
- Should not be used in patients with a history of severe hypersensitivity to exenatide or any product components.

Important Information Regarding a Medullary Thyroid Carcinoma Disease Registry

Amylin is establishing a medullary thyroid carcinoma (MTC) case series registry to systematically monitor the annual incidence of MTC in the United States. This study will be designed to identify if there is any increased risk of MTC related to the introduction of

BYDUREON into the marketplace and will also characterize patient medical histories related to diabetes and use of BYDUREON.

If you have any questions about the MTC registry, please call 1-877-700-7365 or visit www.BYDUREON.com/REMS.

Reporting Adverse Events

To report adverse events among patients taking BYDUREON, contact:

- Amylin (the Sponsor) at 1-877-700-7365 and/or
- FDA's MedWatch Reporting System by phone at 1-800-FDA-1088, or online at www.fda.gov/medwatch/report.htm.

This letter is not intended as a complete description of the risks associated with the use of BYDUREON. Please refer to the enclosed full Prescribing Information and Medication Guide for a complete description of risks.

Please contact our Medical Information department at 1-877-700-7365 if you have any questions about the information in this letter or the safe and effective use of BYDUREON.

Sincerely,

Lisa Porter, M.D.
Vice President, Research and Development
Amylin Pharmaceuticals, Inc.

Enclosure: BYDUREON™ (exenatide extended-release for injectable suspension) Full Prescribing Information (version)

Appendix 2: Highlighted Information for Prescribers

HIGHLIGHTED INFORMATION FOR PRESCRIBERS

BYDUREON™ (exenatide extended-release for injectable suspension)

This information is being provided as part of the Risk Evaluation and Mitigation Strategy (REMS) plan for BYDUREON. REMS plans have been required for certain drugs with serious risks since 2008 by the U.S. Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh the risks. FDA has determined that a REMS is necessary to ensure that the benefits of BYDUREON outweigh the potential risk of medullary thyroid carcinoma and the risk of acute pancreatitis. Amylin Pharmaceuticals, Inc. has established an informational program for healthcare professionals to help minimize these risks.

There is a Boxed Warning for BYDUREON:

WARNING: RISK OF THYROID C-CELL TUMORS

Exenatide extended-release caused an increased incidence in thyroid C-cell tumors at clinically relevant exposures in rats compared to controls. It is unknown whether exenatide extended-release causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be determined by clinical or nonclinical studies. BYDUREON is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with BYDUREON. Patients should be counseled regarding the risk and symptoms of thyroid tumors.

Potential Risk of Medullary Thyroid Carcinoma (MTC)

- Patients with thyroid nodules noted on physical examination or neck imaging should be referred to an endocrinologist for further evaluation.
- 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 BYDUREON. 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.

Risk of Acute Pancreatitis

- Based on postmarketing data exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis.

- After initiation of BYDUREON, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting).
- If pancreatitis is suspected, BYDUREON should promptly be discontinued, confirmatory tests should be performed, and appropriate management should be initiated.
- If pancreatitis is confirmed, BYDUREON should not be restarted.
- Consider other antidiabetic therapies in patients with a history of pancreatitis (b) (4)

Appropriate Patient Selection

BYDUREON:

- Is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- Is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.
- Has not been studied in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis while using BYDUREON. (b) (4) in patients with a history of pancreatitis.
- Should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
- Has not been studied in combination with insulin and concurrent use is not recommended.
- Should not be used in patients with a history of severe hypersensitivity to exenatide or any product components.

Patients should be informed of the potential risks and benefits of BYDUREON and of alternative modes of therapy.

Patients should be advised to read the Medication Guide before starting BYDUREON and review the information each time their prescription is refilled.

Important Information Regarding a Medullary Thyroid Carcinoma (MTC) Disease Registry

Amylin is establishing a medullary thyroid carcinoma (MTC) case series registry to systematically monitor the annual incidence of MTC in the United States. This study will be designed to identify if there is any increased risk of MTC related to the introduction of BYDUREON into the marketplace and will also characterize patient medical histories related to diabetes and use of BYDUREON.

If you have any questions about the MTC registry, please call 1-877-700-7365 or visit www.BYDUREON.com/REMS.

Indication

The FDA has approved BYDUREON as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

16 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JOYCE P WEAVER
12/23/2011

CLAUDIA B KARWOSKI
12/23/2011
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

Interim Comments on Risk Evaluation and Mitigation Strategy (REMS) Set # 1

Date:	December 5, 2011
Reviewer(s):	Joyce Weaver, Pharm.D., Risk Management Analyst Anahita Tavakoli, M.A., Health Communications Analyst Division of Risk Management (DRISK)
Team Leader:	Cynthia LaCivita, Pharm.D., DRISK
Division Director:	Claudia Karwoski, Pharm.D., DRISK
Drug Name(s):	Bydureon, exenatide extended-release
Therapeutic Class:	Glucagon-like peptide-1 (GLP-1) receptor agonist
Dosage and Route:	2 mg subcutaneous injection once weekly
Application Type/Number:	022-200
Submission Number:	DARRTS # 43, EDR serial # 34
Applicant/sponsor:	Amylin Pharmaceuticals, Inc
OSE RCM #:	2011-2836

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1 INTRODUCTION

The following are regulatory milestones pertinent to the REMS for Bydureon:

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- February 16, 2010—The FDA sent a REMS letter to the sponsor notifying of the need for a REMS comprising a Medication Guide (MG) + communication plan (CP) to ensure the benefits of Bydureon outweigh its risks of medullary thyroid carcinoma and acute pancreatitis, including necrotizing and hemorrhagic pancreatitis. The letter specified that the CP should include a Dear Healthcare Professional (DHCP) letter, a Direct Mail letter, a document with highlighted info for prescribers, and a website.
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- July 28, 2011—The application was resubmitted; the resubmission included a REMS submission comprising a CP.

2 MATERIALS REVIEWED

REMS proposal in submission of July 28, 2011

3 SUMMARY OF APPLICANT'S PROPOSED REMS

The goal of the REMS is to inform providers about the risk of acute pancreatitis (including necrotizing and hemorrhagic pancreatitis) and the potential risk of medullary thyroid carcinoma associated with Bydureon. The REMS elements include a communication plan and timetable for submission of assessments (1, 2, 3

and 7 years). Based on advice from the Agency, the communication plan included a DHCP letter, a Direct Mail letter, and a document containing highlights of the safety information ("Highlighted Information for Prescribers"). The communication plan targets likely prescribers of Bydureon, based on previous prescribing of Byetta, the twice-daily formulation of exenatide.

The DHCP letter was to be sent the sooner of, within 60 days of approval or at the time of launch. The Direct Mail letter was to be sent once yearly for three years. The Highlighted Information for Prescribers was to be mailed with the Direct Mail letter, and was to be presented to Healthcare Professionals (HCPs) by Amylin staff when detailing HCPs on Bydureon.

The REMS assessments were scheduled at 1, 2, 3, and 7 years. The assessment reports will include details regarding how many HCPs received the letters, and the results of HCP understanding of the risks.

4 RECOMMENDATIONS FOR THE REVIEW DIVISION

We recommend that the following comments on the Bydureon REMS proposal be sent to the applicant. Please request that the applicant respond to these comments as soon as possible to facilitate further review within the Prescription Drug User Fee Act (PDUFA) deadline for this NDA submission.

The comments below are based on DRISK's preliminary review of the REMS proposal for Bydureon. Appended to this review are the REMS proposal, REMS materials, and the REMS supporting document, including our track changes. The applicant should be reminded that the REMS Supporting Document must be consistent with all changes made to the REMS document.

5 COMMENTS FOR THE APPLICANT

5.1 COMMUNICATION PLAN

We recommend that the Direct Mail letter be eliminated from the REMS. We propose that the DHCP letter be sent twice, 6 months apart, via electronic mail (email). Standard mail and facsimile should be employed to reach HCPs not reachable by email.

The DHCP should be sent to relevant professional organizations for distribution to their members. At the same time the letter is supplied to professional organizations, it should be sent to MedWatch.

5.2 TIMETABLE FOR SUBMISSION OF ASSESSMENTS

We recommend that assessments be conducted at 1 and 2 years.

5.3 INFORMATION NEEDED FOR ASSESSMENT

In addition to surveys to assess understanding, the assessment report should include the number and specialty of HCPs reached via email, the number and specialty of HCPs who opened the email, the names of professional organizations contacted to distribute the DHCP letter to their members, the names of the organizations who accepted and

redistributed the letter, and the names of the professional organizations who declined to accept or redistribute the DHCP letter.

Additionally, the assessment report should include data and analysis establishing whether Bydureon is being used as first-line therapy.

5.4 GENERAL COMMENTS

Resubmission Requirements and Instructions: Submit the revised proposed REMS for Bydureon with attached materials and the REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

Format Request: Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single MS Word document.

6 REMS SUPPORTING DOCUMENT

The REMS Supporting Document must be consistent with all changes made to the REMS document.

ATTACHMENTS

REMS and REMS Supporting Document with track changes

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/s/

JOYCE P WEAVER
12/06/2011

CYNTHIA L LACIVITA
12/06/2011
Concur

REMS Interim Review Comments

Drug Name:	**BLA/NDA:**	**Date:** September 21, 2010
Bydureon® (exenatide extended-release for injectable suspension)	NDA 022200	**Comment Set # 1**
DRISK Scientific Lead: LCDR Kendra Worthy, Pharm.D., Risk Management Analyst		**Reviewers:** • Kate Heinrich, MA, Health Education Reviewer (DRISK) • Suzanne Robottom, Pharm.D., Risk Management Analyst Team Leader (DRISK)
RCM #: 2009-1052		

Materials Reviewed:

- Bydureon (exenatide extended-release for injectable suspension) draft labeling dated July 9, 2010.
- Amylin Pharmaceuticals, Inc. proposed REMS (including proposed REMS, Communication Plan materials and REMS Supporting Document), dated April 22, 2010.
- Amylin Pharmaceuticals Cover Letter re: Complete Response resubmission, dated April 22, 2010.
- FDA Complete Response to Amylin Pharmaceuticals, NDA 022200 Bydureon (exenatide), dated March 12, 2010.
- FDA REMS Notification Letter to Amylin, dated February 16, 2010.
- Novo Nordisk approved Victoza REMS and REMS Supporting Document dated January 25, 2010.

Comments to DMEP:

The comments below are DRISK's preliminary review of the proposed REMS for Bydureon (exenatide) extended-release for injectable suspension. Please request that the sponsor respond to these comments within 2 weeks to facilitate further review.

We included a comment to the sponsor (3.G.a) requesting that they include information about the medullary thyroid cancer disease registry in the brochure, including contact information for further information about the registry. We wanted to confirm the utility of this comment, being that the registry information may not be finalized at this time. Remove this comment if it is not necessary to communicate information about the registry.

Attached to this review (in Appendix A) includes an edited (with track changes) Proposed REMS, including the DHCP Letter and Direct Mail Letter. In addition to the comments below, please send the attachments to the sponsor as well.

Comments to the Sponsor:

REMS

1. REMS Goals:

Revise REMS goals as follows:

- To inform providers about the risk of acute pancreatitis (including necrotizing pancreatitis) and the potential risk of medullary thyroid carcinoma associated with Bydureon.

- To educate patients about the serious risks associated with Bydureon.

2. Medication Guide

A. Comments on the content of the Medication Guide are provided separately.

3. Communication Plan:

Revise the Communication Plan as follows. All revisions should be made to the REMS and the REMS Supporting Document.

A. A definite time period, including initiation date and end date, is needed in the communication plan for all communication activities. Currently you propose the DHCP letter to be sent out within 60 days of product launch, with no parameters for a launch date. We recommend sending the letter within a set timeframe, for example, within 60 days of approval of Bydureon or in conjunction with product launch, whichever is sooner.

B. Broaden the intended audience of the communication plan to include all endocrinologists. Provide more detail about how the intended audience will be derived (which databases, numbers of healthcare professionals by specialty, etc…) for the healthcare professionals that are likely to prescribe Bydureon as well as all endocrinologists.

C. Any new prescribers of Bydureon should also be targeted in the communication plan. Revise the dissemination strategy to identify and reach new prescribers regardless of use or specialty for 3 years after product launch. These details should be included in the REMS and the REMS Supporting Document.

D. The follow-up Direct Mailer and Highlighted Information for Prescribers should be updated if labeling changes for the risks outlined in the REMS are approved. Include this information in the Supporting Document.

E. DHCP Letter
   a. See letter with suggested track changes in Appendix B.
   b. Submit the revised DHCP Letter.

F. Direct Mail Letter
   a. See letter with suggested track changes in Appendix C.
   b. Submit the revised Direct Mail Letter.

G. Highlighted Information for Prescribers
   a. Include information about the medullary thyroid cancer disease registry in the brochure, including contact information for further information about the registry.
   b. Incorporate relevant revisions from the DHCP Letter into the Highlighted Information for Prescribers.

   c. Submit the revised Highlighted Information for Prescribers.

H. REMS specific link on Bydureon website
   a. The goals listed on the website should reflect the goals in the approved REMS.

4. Timetable for Assessment of the REMS:

A. Proposed Timetable: We recommend the following language, which is from the draft guidance, *"Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications"*:

Amylin Pharmaceuticals, Inc. will submit REMS Assessments to FDA at 1 year, 2 years, 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. Amylin Pharmaceuticals, Inc. will submit each assessment so that it will be received by the FDA on or before the due date.

REMS Supporting Document

1. Revise the Supporting Document to be consistent with the REMS.

General Comments

1. Submit the revised Proposed REMS with appended materials and the REMS Supporting Document. Provide a track changes and clean version of all revised materials and documents.

2. Format Request: Please submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS and appended materials be a single WORD document. If certain documents are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single WORD document.

3. We note that the surveys and methodologies for REMS assessment have not been submitted and your intent to submit them to FDA at least 90 days before you plan to conduct the evaluation. The submission should be coded "REMS Correspondence".

    A. We remind you to submit final methodology and instruments that were used to evaluate the effectiveness of the REMS with your required assessments.

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/s/

KENDRA C WORTHY
10/05/2010

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:	22200
Products:	BYDUREON (exenatide for injectable suspension), 2 mg
APPLICANT:	Amylin Pharmaceuticals, Inc.
FROM:	Mary H. Parks, M.D.
DATE:	1 February 2010

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a 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 BYDUREON (exenatide for injectable suspension) to ensure that the benefits of the drug outweigh the potential serious risk of medullary thyroid carcinoma identified in non-clinical studies, and a signal of a serious risk of acute pancreatitis, including necrotizing and hemorrhagic pancreatitis identified in postmarketing reports for the currently approved formulation of exenatide injection, BYETTA®.

In reaching this determination we considered the following:

A. Approximately 24 million people in the United States have type 2 diabetes of whom more than one-third will require more than one anti-diabetic agent to maintain adequate glycemic control within several years of initiation of drug therapy. In 2008, approximately (b) (4) patients filled a prescription for the currently approved formulation of exenatide injection, BYETTA®.

B. Patients with type 2 diabetes who require anti-diabetic medication for glycemic control are at risk for a variety of complications including heart disease, stroke,

blindness, kidney failure, nervous system damage, amputations, and death if untreated.

C. BYDUREON (exenatide for injectable suspension) has been shown to achieve a mean reduction from baseline in hemoglobin A1c over 30 weeks of approximately 1.9%. Some of the complications listed above can be prevented or delayed with good glycemic control. BYDUREON (exenatide for injectable suspension) 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 acute pancreatitis, including necrotizing and hemorrhagic pancreatitis, BYDUREON (exenatide for injectable suspension) is associated with the following other adverse effects, including gastrointestinal adverse events such as nausea and diarrhea, serious, hypoglycemia especially when used with an insulin secretagogue (e.g., a sulfonylurea), hypersensitivity, renal failure, and injection site reactions.

F. BYDUREON (exenatide for injectable suspension) is not a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for BYDUREON (exenatide for injectable suspension). FDA has determined that BYDUREON (exenatide for injectable suspension) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of BYDUREON (exenatide for injectable suspension). FDA has determined that BYDUREON (exenatide for injectable suspension) is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use BYDUREON (exenatide for injectable suspension).

The elements of the REMS will be a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22200	ORIG-1	AMYLIN PHARMACEUTICALS INC	EXENATIDE LAR

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/s/

AMY G EGAN
02/16/2010

MARY H PARKS
02/16/2010