

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022200Orig1s000**

**REMS**

**NDA 022-200**

**Initial REMS approval mm/yyyy**

**BYDUREON™ (exenatide extended-release for injectable suspension)**

**A glucagon-like peptide-1 (GLP-1) receptor agonist**

**Amylin Pharmaceuticals, Inc.**

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**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 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 1 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 1 year after the initial date of approval.

The BYDUREON REMS web page 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, 2 years and in the 7<sup>th</sup> 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 not 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 causes an increased incidence in thyroid C-cell tumors at clinically relevant exposures in rats compared to controls. It is unknown whether BYDUREON 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.

### **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. Consider other antidiabetic therapies 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](http://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](http://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 causes an increased incidence in thyroid C-cell tumors at clinically relevant exposures in rats compared to controls. It is unknown whether BYDUREON 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.

### **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. Consider other antidiabetic therapies 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](http://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.

### Appendix 3: REMS-specific Link on BYDUREON Website – Landing Screen Shot

Important Safety Information | Prescribing Information | Medication Guide

**BYDUREON™**  
exenatide extended release for  
injectable suspension

## Risk Evaluation and Mitigation Strategy

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

TO ASSURE THE BYDUREON IS PREPARED AND TAKEN SAFELY, Amylin has developed materials to inform patients and healthcare providers about the risk of acute pancreatitis and the potential risk of medullary thyroid carcinoma associated with the use of BYDUREON. To learn more about these serious risks, read the Medication Guide posted in the links below, including the Important Safety Information.

The goals of the BYDUREON REMS are:

- To inform providers about the risk of acute pancreatitis (including severity and mortality, pancreatitis) and the potential risk of medullary thyroid carcinoma associated with BYDUREON.
- To educate patients about the serious risks associated with BYDUREON.

To learn more, download these important documents:

- ⇒ REMS for BYDUREON
- ⇒ Dear Healthcare Professional Letter
- ⇒ Prescribing Information
- ⇒ Medication Guide
- ⇒ Highlighted Information for Prescribers
- ⇒ MTC Regulatory Information

[Indication and Usage](#)

**Pending Final Package Insert**

**Important Safety Information for BYDUREON™ (exenatide extended-release for injectable suspension)**

**Pending Final Package Insert**

Prescribing Information | Medication Guide | Contact Us

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARY H PARKS  
01/27/2012