

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-919

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

NDA 21-773, 21-919

BYETTA (exenatide) injection
(glucagon-like peptide (GLP)-1 receptor agonist)

Amylin Pharmaceuticals, Inc.
9360 Towne Centre Drive
San Diego, CA 92121

Contact Information:
Orville Kolterman, M.D.
Senior Vice President, Research & Development
858-642-7153

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS FOR RISK MITIGATION

A. Pancreatitis: To mitigate the potential risk of undiagnosed and/or complicated pancreatitis associated with BYETTA (exenatide) by:

1. Raising the level of patient and healthcare professional (HCP) awareness of:
(i) the signs and symptoms of pancreatitis, including necrotizing and hemorrhagic pancreatitis; and (ii) how to distinguish between common gastrointestinal adverse reactions of BYETTA (exenatide) (nausea, vomiting) versus the hallmark symptom of pancreatitis, which is severe and persistent abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting;
2. Informing HCPs of the importance of timely evaluation of patients for possible pancreatitis when they present with symptoms.

B. Renal Failure: To mitigate the potential risk of renal failure associated with BYETTA (exenatide) by:

1. Raising the level of patient and HCP awareness of: (i) the signs and symptoms of newly developed or worsening renal impairment; and (ii) when to use caution in treating patients with renal impairment.

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be enclosed with each BYETTA (exenatide) prescription in accordance with 21 CFR 208.24. The Medication Guide is enclosed within each BYETTA carton at the time of final product assembly along with the Prescribing Information and User Manual.

The Medication Guide is appended as [Appendix 1](#).

B. Communication Plan

In accordance with FDCA 505-1(e)(3), Amylin will implement the following elements of a communication plan to HCPs likely to prescribe BYETTA (exenatide):

A Dear HCP (DHCP) Letter will be distributed concurrent with implementation of the revised product labeling. The letter will also be available via a link from the BYETTA (exenatide) website and through the medical information department. The intended audience for this letter is HCPs who are likely to prescribe BYETTA (exenatide) as well as pharmacists likely to dispense BYETTA (exenatide). This audience will be HCPs who have written at least one BYETTA (exenatide) 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, as well as all retail pharmacists. The DHCP letter is appended as [Appendix 2](#).

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

REMS Assessments will be submitted to FDA no later than 18 months, 3 years, and, if necessary, 7 years following the date of the REMS approval by FDA.

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 will submit each assessment so that it will be received by the FDA on or before the due date.

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

/s/

AMY G EGAN
10/29/2009
Amy Egan for Mary Parks

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: October 21, 2009

To: John Bishai, Ph.D. – Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products (DMEP)

From: Samuel M. Skariah, Pharm.D. – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: NDA 21-919
DDMAC comments on the draft Dear Healthcare Provider Letter for Byetta® (exenatide) Injection

DDMAC has reviewed the proposed Dear Healthcare Provider (DHCP) Letter submitted by Amylin Pharmaceuticals, Inc. on October 13, 2009 for Byetta® (exenatide) Injection (Byetta).

DDMAC notes the following statement will be removed from the final version of the DHCP letter:

 (b) (4)

DDMAC offers the following comments:

1. We recommend communicating the full indication for Byetta, including the full important limitations for use, within the proposed DHCP letter.
2. In addition, we recommend communicating that Byetta is also associated with the following important risks, within the proposed DHCP letter:
 - a. Hypoglycemia: Increased risk when BYETTA is used in combination with a sulfonylurea.

- b. Renal Impairment: Postmarketing reports, sometimes requiring hemodialysis and kidney transplantation. BYETTA should not be used in patients with severe renal impairment or end-stage renal disease and should be used with caution in patients with end-stage renal disease. Caution should be applied when initiating BYETTA or escalating the dose of BYETTA in patients with moderate renal failure.
- c. Severe Gastrointestinal Disease: Use of BYETTA is not recommended in patients with severe gastrointestinal disease.
- d. Immunogenicity: Patients may develop antibodies to exenatide following treatment with BYETTA, consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals.
- e. Hypersensitivity: There have been postmarketing reports of serious hypersensitivity reactions (e.g. anaphylaxis and angioedema) in patients treated with BYETTA.
- f. Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with BYETTA or any other antidiabetic drug.
- g. Most common ($\geq 5\%$) and occurring more frequently than placebo in clinical trials: nausea, hypoglycemia, vomiting, diarrhea, feeling jittery, dizziness, headache, dyspepsia.

Thank you for the opportunity to comment on this proposed DHCP letter. If you have any questions, please contact me at 301.796.2774 or Sam.Skariah@fda.hhs.gov.

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

/s/

SAMUEL M SKARIAH
10/21/2009