



NDA 21-919
NDA 21-773/S-009, S-011, S-017, S-018, S-022, S-025

**NDA APPROVAL
SUPPLEMENT APPROVAL**

Amylin Pharmaceuticals, Inc.
Attention: Orville Kolterman, M.D.
Senior Vice President, Research & Development
9360 Towne Centre Drive
San Diego, CA 92121

Dear Dr. Kolterman:

Please refer to your June 29, 2004, new drug application (NDA) 21-919 submitted under section 505(b) of the Federal Food Drug, and Cosmetic Act (FDCA) for Byetta (exenatide) Injection.

We acknowledge receipt of your submissions dated May 5, 2005, January 3, July 2 and 31, 2007, March 19, June 6 and 23, July 29, and August 8 and 25, September 11 and 18 (2), October 10, November 5 and 12, and December 19, 2008, and January 5 and 16, February 5 and 13, March 19, August 7, September 3, 4, 11, 24, and 28, and October 5, 16, and 30, 2009.

The March 19, 2008, submission constituted a complete response to our April 28, 2005, action letter.

This new drug application provides for the use of Byetta (exenatide) Injection as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Please also refer to your supplemental new drug applications to NDA 21-773 submitted under section 505(b) of the FDCA for Byetta (exenatide) as combination therapy with other antidiabetic agents, as follows:

<u>sNDA</u>	<u>Submission Date</u>	<u>Type</u>	<u>Provides for</u>	<u>Pieces of Labeling</u>
S-009	March 28, 2007	Prior Approval Labeling Supplement	Language regarding the use of oral contraceptives	Package Insert and Patient Package Insert
S-011	September 20, 2007	Changes Being Effected Labeling Supplement	Language regarding altered renal function	Package Insert and Patient Package Insert
S-017	September 3, 2008	Prior Approval Labeling Supplement	Language regarding postmarketing cases of necrotizing and hemorrhagic pancreatitis	Package Insert and Patient Package Insert
S-018	November 18, 2008	Changes Being Effected Labeling Supplement	Improved readability of lot number and expiration date on pen label	5 mcg and 10 mcg pen labels
S-022	June 12, 2009	Changes Being Effected Labeling Supplement	Modification of the color block on the third panel of the pen carton labels	5 mcg and 10 mcg carton labels
S-025	October 16, 2009	Prior Approval Supplement	Proposed Risk Evaluation and Mitigation Strategy	Proposed REMS & REMS supporting document

We have completed our review of these applications (NDA 21-919 and the supplements to NDA 21-773), as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 9 years (inclusive) because necessary studies are impossible or highly impractical. This is because the number of pediatric patients is so small.

We are deferring submission of your pediatric study for ages 10 to 16 years (inclusive) until December 31, 2010 because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric study required by section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. This required study is listed below.

1559-1: Deferred pediatric study under PREA for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 16 years (inclusive).

Final Report Submission: **December 31, 2010**

Submit all final study reports to NDA 21-773. Use the following designator to prominently label all submissions:

Required Pediatric Assessment

NEW SAFETY INFORMATION

Section 505(o) and Section 505-1 of the FDCA authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)) and to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

Since Byetta (exenatide) was approved on April 25, 2005, we have become aware of postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, and postmarketing reports of acute renal failure, sometimes leading to death or transplantation, in patients taking Byetta (exenatide). We have also become aware of postmarketing reports of thyroid neoplasms associated with the use of Byetta (exenatide) and of a signal of thyroid neoplasms observed pre-clinically with other GLP-1 analogues. We consider this information to be “new safety information” as defined in section 505-1(b)(3) of the FDCA.

After consideration of this new safety information, we have determined that postmarketing requirements are needed to assess the risk of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, and the risk of thyroid neoplasms, and that a REMS is necessary for Byetta (exenatide) to ensure that the benefits of the drug outweigh the risks of acute pancreatitis and acute renal failure. These requirements are described more fully below.

POSTMARKETING REQUIREMENTS UNDER 505(o)

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of a serious risk of acute pancreatitis, including hemorrhagic or necrotizing pancreatitis, and the signal of a serious risk of thyroid neoplasms.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

1559-2: An adequately powered epidemiological study to determine the incidence rate, severity and risk factors for the development of acute pancreatitis, including the more severe forms of hemorrhagic and necrotizing pancreatitis, in exenatide-exposed versus unexposed patients.

The timetable you submitted on September 11, 2009, states that you will submit this study report according to the following timetable:

Final Report Submission: November 30, 2009

1559-3: Epidemiologic queries using i3 Aperio to assess the relative risk of pancreatic cancer and thyroid neoplasm among patients using Byetta and those using metformin or glyburide. Thyroid neoplasm assessment will also include benign and malignant diagnosis event stratification.

The timetable you submitted on September 18, 2009, states that you will submit this study report according to the following timetable:

Final Report Submission: March 31, 2010

1559-4: A 3-month pancreatic safety study in a diabetic rodent model treated with Byetta.

The timetable you submitted on September 30, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission: March 31, 2010
Study Completion Date: June 30, 2010
Final Report Submission: January 31, 2011

1559-5: Submission of all amylase and lipase data obtained in ongoing, terminated, and completed clinical trials of Byetta, as well as analyses of those data. Also provide a systematic analysis of amylase and lipase data from those patients who presented with abdominal pain or nausea, with or without vomiting, during the treatment phase of those trials.

The timetable you submitted on August 7, 2009, states that you will conduct this study according to the following timetable:

Study Completion Date:	October 27, 2009
Final Report Submission:	March 31, 2010

Finally, we have determined that a clinical trial (in addition to a nonclinical or observational study) will be necessary to fully assess the signal of a serious risk of hemorrhagic or necrotizing pancreatitis. Byetta (exenatide) may decrease gall bladder motility, predisposing patients to gall bladder sludge or gallstone formation, and thus pancreatitis.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

1559-6: A clinical trial investigating the effects of exenatide on CCK (cerulitide)-stimulated gallbladder emptying (as an indirect measure of a potential impact on the sphincter of Oddi) to assess any non-physiologic effects of exenatide on biliary emptying.

The timetable you submitted on October 19, 2009, states that you will submit this trial report according to the following timetable:

Final Report Submission:	December 31, 2010
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Submit the protocol to your IND, with a cross-reference letter to NDA 21-773. Submit all final reports to NDA 21-773. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Byetta (exenatide) to ensure the benefits of the drug outweigh the risks of acute pancreatitis and acute renal failure. The REMS is being approved for both new drug applications, NDA 21-773 and NDA 21-919.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Byetta (exenatide) 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 Byetta (exenatide). FDA has determined that Byetta 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 Byetta (exenatide).

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Byetta (exenatide).

We have also determined that a communication plan is necessary to support implementation of the REMS.

Your proposed REMS, submitted on October 16, 2009, and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include but is not limited to the following:

- A. Evaluation of patients' understanding of the serious risks of Byetta (exenatide)
- B. Evaluation of healthcare providers' understanding of the serious risks of Byetta (exenatide)
- C. Evaluation of the use of Byetta in patients with underlying renal impairment
- D. Evaluation of healthcare providers' awareness of the need for prompt evaluation of patients who develop symptoms suggestive of pancreatitis
- E. Evaluation of the identification and treatment of acute pancreatitis after initiation of Byetta

- F. 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

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 21-773 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 21-773
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 21-773
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your March 19, 2008 submission informing the Agency that the final printed carton and container labels for NDA 21-919 will be the same as those used in NDA 21-773 for Byetta (exenatide) Injection. A carton and container revision was received on October 10, 2008, which included additional language related to the Medication Guide. We acknowledge your September 24 and October 30, 2009 submissions containing final printed carton and container labels.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the submitted labeling (package insert submitted October 5, 2009, User Manuals submitted October 5, 2009, Medication Guide submitted October 5, 2009). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, “**SPL for approved NDA 21-919 and NDA 21-773/S-009, S-011, S-017, S-018, S-022.**”

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac. We remind you that the REMS pieces are not advertisements or promotional labeling that require submission to DDMAC via Form FDA 2253.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue an additional letter communicating important safety related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch
Food and Drug Administration

Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

We request that for a period of two years, you submit all cases of pancreatitis and renal failure as 15-day alert reports and that you provide analyses of clinical trial and post-marketing reports of pancreatitis and renal failure as adverse events of special interest in your periodic safety update reports.

All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDA 21-773 for this drug product, not to this NDA. In the future, do not make submissions to NDA 21-919 except for the final printed labeling requested above.

If you have any questions, call John Bishai, Ph.D., Regulatory Project Manager, at (301) 796-1311.

Sincerely,

{See appended electronic signature page}

Mary Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration

Enclosures:
Package Insert
Medication Guide
Pen Carton Labels (5 mcg and 10 mcg)
Pen Container Labels (5 mcg and 10 mcg)
User Manuals (5 mcg and 10 mcg)
REMS

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21773	SUPPL-9	AMYLIN PHARMACEUTICA LS INC	BYETTA (EXENATIDE) INJ,SOL 0.25MG/ML
NDA-21773	SUPPL-11	AMYLIN PHARMACEUTICA LS INC	BYETTA (EXENATIDE) INJ,SOL 0.25MG/ML
NDA-21773	SUPPL-17	AMYLIN PHARMACEUTICA LS INC	BYETTA (EXENATIDE) INJ,SOL 0.25MG/ML
NDA-21773	SUPPL-18	AMYLIN PHARMACEUTICA LS INC	BYETTA (EXENATIDE) INJ,SOL 0.25MG/ML
NDA-21773	SUPPL-22	AMYLIN PHARMACEUTICA LS INC	BYETTA (EXENATIDE) INJ,SOL 0.25MG/ML
NDA-21773	SUPPL-25	AMYLIN PHARMACEUTICA LS INC	BYETTA (EXENATIDE) INJ,SOL 0.25MG/ML

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/s/

MARY H PARKS
10/30/2009