

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-919

OTHER ACTION LETTER(s)



NDA 21-919

Amylin Pharmaceuticals, Inc.
Attention: John Wood, MBA, RAC
Senior Director, Regulatory Affairs
9360 Town Centre Drive, Suite 110
San Diego, CA 92121-3030

Dear Mr. Wood:

Please refer to your June 29, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Byetta™ (exenatide) Injection, 250 mcg/mL.

We acknowledge receipt of your submissions dated August 12 and 18, October 28, November 4, and December 17, 2004, and January 27, March 25, and April 8 (2), and 12 (2), 2005.

This new drug application provides for the use of Byetta™ (exenatide) Injection monotherapy to improve glycemic control in patients with type 2 diabetes mellitus.

We have completed our review of this application, as amended, and it is approvable. The single monotherapy study submitted (Study 2993-120, *A Phase 2, Randomized, Triple-Blind, Parallel-Group, Placebo-Controlled, Multicenter Study to Examine the Effect of Exenatide Monotherapy on Glucose Control in Subjects With Type 2 Diabetes Mellitus*) was only 28 days in duration and enrolled only 99 patients. As such, the study was inadequate to characterize the efficacy of exenatide as monotherapy for the treatment of patients with type 2 diabetes mellitus.

Before the application may be approved, it will be necessary for you to submit data from at least one adequate and well-controlled trial of sufficient duration to assess the efficacy (i.e., HbA1c lowering) and safety of exenatide monotherapy in patients with type 2 diabetes mellitus. We recommend that you discuss your planned study with the Division of Metabolic and Endocrine Drug Products.

When you respond to the above deficiency, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - a. Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

- b. Present tabulations of the new safety data combined with the original NDA data.
 - c. Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - d. For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
 4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
 5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
 6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
 7. Provide English translations of current approved foreign labeling not previously submitted.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Metabolic and Endocrine Drug Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed for the monotherapy indication until you have been notified in writing that the application is approved.

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If you have any questions, call Lina AlJuburi, Regulatory Project Manager, at (301) 827-6414.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.

Director

Office of Drug Evaluation II

Center for Drug Evaluation and Research

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

/s/

Robert Meyer

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