

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022200Orig1s000

OTHER ACTION LETTERS



NDA 022200

COMPLETE RESPONSE

Amylin Pharmaceuticals, Inc.
Attention: Orville Kolterman, M.D.
Sr. Vice President, Research & Development
9360 Towne Centre Drive, Suite 110
San Diego, CA 92121

Dear Dr. Kolterman:

Please refer to your new drug application (NDA) dated and received May 4, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for BYDUREON (exenatide for injectable suspension).

We acknowledge receipt of your amendments dated April 22, May 20, June 2, 21, and 29, July 21, August 25, and September 13 and 30, 2010. The April 22, 2010, submission constituted a complete response to our March 12, 2010, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

On March 12, 2010, the FDA issued a complete response action for NDA 022200 citing product quality deficiencies and the need for a Risk Evaluation and Mitigation Strategy (REMS). On April 22, 2010, a resubmission was received by FDA that included complete responses to the deficiencies identified in the March 12, 2010 action letter.

On April 12, 2010, FDA was made aware of a thorough QT study (tQT), which took place between April 23, 2008, and July 21, 2008, that was required by Health Canada as part of a New Drug Submission for Byetta that was not conducted under a U.S. IND. Only the title of this study ("A placebo and positive controlled study of the electrophysiological effects of a single 10 mcg dose of exenatide on the 12 lead electrocardiogram (ECG) QT interval in healthy subjects" – Study GWCI) was reported in a table to your IND 057725 in your annual reports dated April 10, 2009 and April 9, 2010. FDA was not informed of these study results or concerns raised by Health Canada during its initial review of NDA 022200. Consequently, the March 12, 2010 complete response letter did not identify this study as a deficiency item to be addressed in NDA 022200. Upon learning of the tQT results, we notified you on April 13, 2010, that the completed results of this study, must be submitted for review with NDA 022200 due to concerns of QT prolongation raised by Health Canada. The report and ancillary documents for Study GWCI were submitted to IND 057725 on April 15 and May 13, 2010, respectively.

Based on our review of Study GWCI, there was a significant concentration-QTc relationship for exenatide. This observation is concerning for NDA 022200 because the mean maximum concentration (C_{max}) of exenatide achieved in this study was approximately half the maximum steady state concentration (C_{max,ss}) observed for Bydureon after 2 mg administration. Furthermore, population PK analysis of patients with mild-to-moderate renal impairment receiving exenatide 2 mg once weekly revealed a 50-60% higher exposure in these patients compared to that in patients with normal renal function. In the absence of a positive control, QT data collected in your phase 3 study are not adequate to rule out small drug-induced QT changes. In contrast to Study GWCI, the intrinsic variability in the measurement of QT interval in the phase 3 trial is not well controlled and small drug-induced increases might not be detected. Furthermore, the number of patients with moderate impairment exposed to Bydureon in NDA 022200 is inadequate (n=10) to address this safety concern.

1. To address this deficiency, you will need to conduct a tQT study following treatment with exenatide at exposures comparable to those observed in renal impaired patients taking Bydureon. Prior to conducting the tQT study, the protocol should be submitted to the Agency for review.

In our original review of Study LAR-105 titled, "A Randomized, Open-Label, Multicenter Comparator-Controlled Study to Examine the Effects of Exenatide Long-Acting Release on Glucose Control (HbA1c) and Safety in Subjects with Type 2 Diabetes Mellitus Managed with Diet Modification and Exercise and/or Oral Antidiabetic Medications", in NDA 022200, we noted that exenatide 2 mg once weekly resulted in a statistically significantly greater reduction in HbA1c compared to Byetta 10 mcg bid. The difference in adjusted mean change in HbA1c was -0.3 with an accompanying 95% CI of -0.5 to -0.1. However, this study did not evaluate the commercial drug product. Instead, a comparability substudy to LAR-105 titled LAR-105c, was conducted after Week 30 to compare clinical effectiveness between the investigational product and the commercial product. In this substudy, both investigational and commercial drug products increased HbA1c with greater deterioration in glycemic control observed with the commercial product. The average difference between the two products was 0.2 after 18 weeks of treatment with an accompanying 95% CI for this comparison of 0.0 to 0.3. The lower bound of this 95% CI raises concern that the commercial product may be less effective than the investigational product used in LAR-105. As a result, we can not conclude that the commercial product will provide superior efficacy to the currently marketed Byetta from LAR-105.

2. We have recently been notified by you that the completed Study LAR-108 titled, "A Randomized, Open-Label, Parallel-Group, Comparator-Controlled, Multicenter Study to Evaluate the Glycemic Effects, Safety, and Tolerability of Exenatide Once Weekly in Subjects with Type 2 Diabetes Mellitus," has a similar study design to Study LAR-105 but employs the commercial drug product. The results of Study LAR-108 should be submitted with your tQT study to enable a more accurate evaluation of the efficacy of Bydureon and labeling of the safety and effectiveness of Bydureon.

LABELING

3. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

As described in our letter dated February 16, 2010, in accordance with section 505-1 of the FDCA, we have determined that a risk evaluation and mitigation strategy (REMS) is necessary for BYDUREON (exenatide for injectable suspension) to ensure that the benefits of the drug outweigh the risks of medullary thyroid carcinoma and acute pancreatitis, including necrotizing and hemorrhagic pancreatitis.

We acknowledge the submission of your proposed REMS on April 22, 2010, which contains a Medication Guide, communication plan, and a timetable for submission of assessments of the REMS. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

If you plan to distribute an authorized generic product under this NDA, you will also need to submit a REMS, REMS supporting document, and any required appended documents for that authorized generic, to this NDA. In other words, you must submit a complete proposed REMS that relates only to the authorized generic product. Review and approval of the REMS is required before you may market your product.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials 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:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - 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 trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial 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 updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

POSTMARKETING REQUIREMENTS UNDER 505(o)

As described in our letter dated February 16, 2010 and March 12, 2010, we have determined that, if this application is approved, you will be required to conduct a postmarketing study of BYDUREON (exenatide for injectable suspension) to assess a signal of a serious risk of medullary thyroid carcinoma.

We acknowledge receipt of your submissions dated May 20, 2010 and June 21, 2010 containing your proposed postmarketing study to address this issue. We will continue discussion of your postmarketing study proposal as needed.

Any additional specific details of this required postmarketing study, including a timetable and annual reporting requirements, will be described more fully in the approval letter for this application, if it is approved.

If you complete this study prior to re-submitting your application, you may include the final report and relevant data sets in your Complete Response submission to facilitate review of the information.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must

fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

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

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

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
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/

MARY H PARKS
10/18/2010



NDA 022200

COMPLETE RESPONSE

Amylin Pharmaceuticals, Inc.
Attention: Orville Kolterman, M.D.
Sr. Vice President, Research & Development
9360 Towne Centre Drive, Suite 110
San Diego, CA 92121

Dear Dr. Kolterman:

Please refer to your new drug application (NDA) dated and received May 4, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for BYDUREON (exenatide for injectable suspension).

We acknowledge receipt of your amendments dated June 17, July 27, August 20, September 1 and 3, October 2 and 26, November 3, 5, 19, and 20, and December 3, 4, 11, and 31, 2009, and January 13, 18, and 29, February 3, 2010, and March 10, 2010.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

1. Deficiencies:



(b) (4)



RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

As described in our letter dated February 16, 2010, in accordance with section 505-1 of the FDCA, we have determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for BYDUREON (exenatide for injectable suspension) to ensure that the benefits of the drug outweigh the risks of medullary thyroid carcinoma and acute pancreatitis, including necrotizing and hemorrhagic pancreatitis. Your application cannot be approved without a REMS; therefore, you must include your proposed REMS as part of your response to the deficiencies cited in this letter. Our letter dated February 16, 2010, provides information about what your proposed REMS must include.

LABELING

3. Submit draft labeling that incorporates revisions in the attached labeling. In addition, submit updated content of labeling [21 CFR 314.50(1)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

4. Please submit draft carton and container labeling revised as follows:

A. *Vial Label: Professional Sample and Trade (2 mg vial)*

1. Revise the established name to read as “exenatide extended-release for injectable suspension” on all container labels and carton labeling.
2. Relocate the product strength to appear beneath the established name.
3. On the professional sample, the dark-green box highlighting the professional sample statement is more prominent than the proprietary name and product strength. Decrease the prominence of the dark-green boxed professional sample statement by lightening the green color and de-bolding the professional sample statement or some other means.
4. Revise the statement “Single dose” to read as: “Single dose. Discard unused portion”.
5. Since the vial label is small, relocate the “Rx Only” statement towards the side of the label and decrease its prominence. In its current presentation, the “Rx Only” statement appears more prominent than the product strength.
6. To accommodate for the small size of the vial label, relocate the word “Sterile” towards the side of the label in order to minimize crowding on the principle display panel.

B. Lid Label: Professional Sample and Trade

1. Increase the prominence of “Once-weekly” on the lid label.
2. Increase the prominence of the product strength and relocate it to appear beneath the established name.

3. On the professional sample, the dark-green box highlighting the professional sample statement is more prominent than the proprietary name and product strength. Decrease the prominence of the dark-green boxed professional sample statement by lightening the green color and de-bolding the professional sample statement or some other means.
4. Relocate the route of administration statement “Subcutaneous use only” to appear closer to the established name to provide more prominence to this statement and in order to avoid this information getting lost amongst all the other information on the label.
5. Consider boxing the statement “Do not substitute the supplies provided” to highlight this information as it is easily lost with all of the other information on the label.
6. Under the description of the kit contents, the bullets concerning the vial, needles, and diluent is vague. For example, the kit is described as containing “1 vial”, but it does not indicate what the vial contains. Additionally, the description of the kit indicates that there are “2 needles” in the kit. The size of the needles is not indicated. Furthermore, the description of the diluent is vague. Provide more information on the vial, needles, and diluent. For example, single-dose kit contains:
 - 1 vial of exenatide or “Bydureon”
 - 2 needles (23 G, 5/16” [include needle gauge and length])
 - 1 x XXmL diluent syringe

C. Diluent Label

1. Increase the prominence of the word “Diluent”, and decrease the prominence of the proprietary name so that users are not confused that the syringe contains any active ingredient (e.g. **Diluent** for suspension of Bydureon). We recommend not using the green text for the Bydureon name. The word “Diluent” should appear more prominent than the word “Sterile” and the “Rx Only” phrase.
2. By presenting the proprietary name on the diluent label in the same manner as it is presented on the carton labeling and container labels, patients may be confused that the diluent syringe already contains active ingredient. Therefore, revise the proprietary name “Bydureon” so it appears in the same font and as the phrase “Diluent for suspension of...”
3. Delete the established name as the diluent does not contain the active ingredient (exenatide for injectable suspension).

D. Carton Labeling: Professional Sample and Trade

1. Revise the established name to read as “exenatide extended-release for injectable suspension” per Chemistry recommendations on all container labels and carton labeling.
2. Increase the prominence of the product strength.
3. Relocate the route of administration statement “Subcutaneous administration only” to appear beneath the established name.

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend that you use one of the following two statements depending upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- “Dispense the enclosed Medication Guide to each patient.” or
- “Dispense the accompanying Medication Guide to each patient.”

SAFETY UPDATE

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

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8. Provide English translations of current approved foreign labeling not previously submitted.

POSTMARKETING REQUIREMENTS UNDER 505(o)(3)

Although not a deficiency, we remind you that, as described in our letter dated February 16, 2010, if this application is approved, you will be required to conduct a postmarketing study of BYDUREON (exenatide for injectable suspension) to assess the signal of a serious risk of medullary thyroid carcinoma. Specifically, we have determined that, if NDA 22200 is approved, you will be required, pursuant to section 505(o)(3) of the FDCA, to conduct the following:

1. A medullary thyroid carcinoma case series registry of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of (exenatide for injectable suspension) into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to diabetes and use of BYDUREON (exenatide for injectable suspension).

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

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Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Package Insert

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22200

ORIG-1

AMYLIN
PHARMACEUTICA
LS INC

Bydureon (exenatide LAR)

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

/s/

MARY H PARKS
03/12/2010