DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021332/S-007 and S-016

SUPPLEMENT APPROVAL

AstraZeneca AB
Attention: Mary E. Whealy
Global Regulatory Affairs Director
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Whealy:

Please refer to your Supplemental New Drug Applications (sNDAs) dated November 29, 2006, received November 30, 2006 (S-007) and dated and received July 20, 2009 (S-016), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Symlin (pramlintide acetate) 600 mcg/ml and 1000 mcg/ml injection.

We acknowledge receipt of your amendments for S-007 dated March 1, May 29, August 10 and October 3, 2007, February 3, May 20, 2009, and June 18, 2010, and March 7, June 30, September 29, 2011, and October 5, 2012, and April 16, 25 (2), and December 5, 2013 and February 20, March 28, and April 30, 2014.

We acknowledge receipt of your amendment for S-016 dated August 25, 2009.

The submission dated February 3, 2009, constituted a complete response to our September 28, 2007, action letter for supplement S-007.

The “Prior Approval” supplemental new drug application (S-007) incorporates the safety information from Study 137-156 in the Symlin Prescribing Information to clarify information regarding the risk of severe hypoglycemia when Symlin (pramlintide acetate) is used concurrently with mealtime insulin.

The “Changes Being Effected” supplemental new drug application (S-016) updates the Symlin (pramlintide acetate) US Prescribing Information and Medication Guide to the required Physician Labeling Rule format (PLR; 21 CFR 201.56), adds postmarketing spontaneous adverse event terms in the "ADVERSE REACTIONS/Post Marketing Experience" section of the PLR, modifies other sections of the labeling to convey proper context for one of the adverse events, and provides similar changes to the Medication Guide in patient-focused language. There is also an administrative change to the Symlin Prescribing Information with the addition of "water for injection" into the DESCRIPTION section of the label.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. 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 provide appropriate annotations, including supplement number(s) and annual report date(s).

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

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 indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

POSTMARKETING COMMITMENTS SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

2163-1 To revise the Instructions for Use section of patient labeling so as to contain additional graphics as previously discussed with the Agency.

The timetable you submitted by email on May 28, 2014, states that you will fulfill this commitment according to the following schedule:

Supplement Submission: November 28, 2014

Submit clinical protocols to your IND 039897 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA 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)]. The details of the REMS requirements were outlined in our REMS notification letter dated April 20, 2010, and in our correspondence dated May 23, 2011, in which we informed you that we had determined that a Medication Guide is not required as part of your proposed REMS.

Your proposed REMS, submitted on March 28, 2014, and appended to this letter, is approved.

The REMS consists of 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:

1. An evaluation of the implementation of REMS Communication Plan activities.
    a. REMS Letters:
        i. The source(s) of the list of healthcare providers and Professional Organizations to whom the REMS Letters were distributed.

ii. Number of health care providers and professional societies targeted by the REMS.

iii. Number of REMS Letters sent to health care providers, stratified by specialty, and professional societies via mail and electronic means (email and/or fax) and the dates the letters were sent. The number of letters sent via postal mail because the health care providers email address was not available or the letter was undeliverable. The number of letters successfully delivered via email. Follow-up with professional societies confirming receipt of the letter and what action, if any, was taken. Dissemination activities performed by the targeted professional societies to their members.

b. REMS Factsheet: number of health care providers detailed, stratified by specialty, and provided the REMS Factsheet through the detail.

c. Scientific meetings: list of scientific meetings in which Symlin REMS information was made available.

d. REMS website: number of unique site visits during the assessment period and cumulative.

2. Evaluation of health care providers' knowledge.

   a. An evaluation of health care providers' knowledge of the risk of severe hypoglycemia associated with the use of Symlin added to mealtime insulin, the importance of insulin dose reduction and the importance of proper patient selection for treatment with Symlin.

   b. Stratify results by medical specialties of health care providers (endocrinology, family/internal medicine, others).

3. Safety Surveillance for the reporting period and cumulatively.

   a. Symlin utilization information including, but not limited to, indication and type of healthcare provider (i.e., endocrinologist, general practitioner, internist, etc.).

   b. Evaluation and post marketing case reports of severe hypoglycemia including use in patients for whom the drug is contraindicated.

   c. Any other relevant data and analysis employed to assess if the Symlin REMS is meeting its goals.

4. With respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal, or whether one or more such goals or such elements should be modified [per section 505-1(g)(3)].

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a

new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 021332 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g., UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

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

NDA 021332 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 021332
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021332
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

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

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form

FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

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

If you have any questions, call Richard Whitehead, Regulatory Project Manager, at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
REMS

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

/s/

JEAN-MARC P GUETTIER
06/27/2014