DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021332/S-024

SUPPLEMENT APPROVAL
REMS ASSESSMENT PLAN REVISION

AstraZeneca AB
Attention: Mary Whealy
Regulatory Affairs Senior Director
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Whealy:

Please refer to your Supplemental New Drug Application (sNDA) dated and received November 20, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Symlin (pramlintide) injection.

We also acknowledge receipt of your amendments dated May 8 and 13, and July 10, 2015.

This supplemental new drug application provides for proposed modifications to the approved Symlin risk evaluation and mitigation strategy (REMS).

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter with the minor editorial revision listed below and reflected in the enclosed REMS:

- Update the Most Recent Modification date on the REMS Document to reflect the date of approval of this supplement.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Symlin (pramlintide) injection was originally approved on June 27, 2014. The REMS consists of a communication plan and a timetable for submission of assessments of the REMS. Your proposed modification to the REMS consists of:

- Changes to the REMS factsheet to the amend the listed adverse event phone number, due to the change in ownership of this NDA
- Changes to the REMS document to:
  - Modify the timeframes in which REMS letters will be sent to certain healthcare providers and professional societies;
  - Remove the requirement that the REMS letter be provided to Medwatch prior to the letter being issued;
  - Modify the timeframe in which the REMS Factsheet will be displayed at certain scientific meetings.

Your proposed modified REMS, submitted on July 10, 2015, and appended to this letter, is approved with the minor editorial revision listed above.

The timetable for submission of assessments of the REMS may remain the same as that approved on June 27, 2014.

We acknowledge receipt of your updated REMS supporting document that includes a description of all proposed modifications and their potential impact on other REMS elements.

The revised REMS assessment plan must include, but is not limited to, the following:

1. An evaluation of the implementation of REMS Communication Plan activities

   The REMS Communication Plan should include the following items for each assessment period and cumulatively:

   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, during the 12-months following initial REMS approval.

   c. Scientific meetings: list of scientific meetings in which SYMLIN REMS information was made available, during the 18-months following initial REMS approval.

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

2. Evaluation of health care providers' knowledge

   AstraZeneca will evaluate via healthcare provider survey healthcare providers' awareness and understanding of the serious risks of SYMLIN including:

   a. An evaluation of health care providers' knowledge of the risk of severe hypoglycemia 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 from the approval of the REMS program

   AstraZeneca will provide:

   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. 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 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.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any of goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that 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). This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that the last assessment and if any modifications of the REMS have been proposed since that assessment.
e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

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 any 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/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 021332/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 021332/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021332/S-000
REMS ASSESSMENT
< other supplement identification >
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 021332

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

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

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, M.S., Regulatory Project Manager, at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Jennifer Rodriguez Pippins, M.D., M.P.H.
Deputy Director for Safety
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
REMS

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

/s/

JENNIFER R PIPPINS
08/07/2015