BLA 125511/S-021

SUPPLEMENT APPROVAL

Shire-NPS Pharmaceuticals, Inc. (now part of Takeda)
Attention: Lauren Mellen
Manager, Global Regulatory Affairs
650 East Kendall Street
Cambridge, MA 02142

Dear Ms. Mellen:

Please refer to your supplemental biologics license application (sBLA), dated and received, November 22, 2019, and your amendments, submitted under section 351(k) of the Public Health Service Act for Natpara (parathyroid hormone) for injection.

This Prior Approval supplemental new drug application provides for proposed modifications to the approved Natpara risk evaluation and mitigation strategy (REMS). This supplement is in response to our July 24, 2019, REMS Modification Notification letter.

We have completed our review of this supplemental application, as amended. It is approved effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Natpara was originally approved on January 23, 2015, and the most recent REMS modification was approved on September 29, 2016. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. In order to minimize burden on the healthcare delivery system of complying with the REMS, we determined that you were required to make the REMS modifications outlined in our REMS Modification letter dated July 24, 2019.

Your proposed modified REMS, submitted on November 22, 2019, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS must be revised to submit REMS Assessments every two years beginning with the REMS assessment for year six (72-month REMS assessment; received, January 22, 2020).

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

1. REMS implementation and operation metrics
   a) Number of prescribers targeted by the REMS by specialty.

b) REMS Website
   i. Number of unique site visits during the assessment period and cumulatively.

c) An assessment of compliance with prescriber certification requirements, including the following:
   i. Number of prescribers certified during the reporting period and cumulatively. Prescriber information, including degree, specialty, and practice setting (i.e., type of practice, geographic location).
   ii. Number of prescriptions for each prescriber.
   iii. Number of prescriptions by specialty.
   iv. Total number and percentage of prescriptions for Natpara that were written by a certified prescriber versus those prescribed by non-certified prescribers.
   v. Number of prescribers who were noncompliant with Natpara REMS Program requirements, detailed description of root cause of noncompliance, and a report of corrective actions taken to address noncompliance including number of prescribers whose certification in the Natpara REMS Program was revoked during the reporting period and cumulatively and the reason for the revocation.

d) An assessment of compliance with pharmacy certification requirements, including the following:
   i. Number of pharmacies certified during the reporting period and cumulatively.
   ii. Total number of orders shipped to pharmacies during the reporting period and cumulatively. Stratify results by pharmacy certification status.
   iii. Total number of prescriptions dispensed during the reporting period and cumulatively. Stratify results by pharmacy certification status.
   iv. Number of pharmacies that were noncompliant with Natpara REMS Program requirements, detailed description of root cause of noncompliance, and a report of corrective and/or preventive actions taken to address noncompliance, including number of pharmacies whose certification in the Natpara REMS Program was revoked during the reporting period and cumulatively and the reason for the revocation.
   v. Report findings of pharmacy audits occurring during the reporting period and cumulatively.
   vi. Report of verification of the authorized representatives for the certified pharmacies.

e) An assessment of compliance with the documentation of safe use condition (i.e., *Natpara REMS Patient-Prescriber Acknowledgment Form*)
   i. The number, age, and gender of patients treated with Natpara during the reporting period and cumulatively (by year). Include a breakdown of ages for all patients under the age of 18.
   ii. Duration of therapy for patients (mean, median, range).
   iii. Total number and percentage of new patients treated with Natpara who had a complete, signed *Natpara REMS Patient-Prescriber*

Acknowledgment Form on record (at the Natpara REMS Program Coordinating Center) versus those who did not.

f) Report findings of distributor audits occurring during the reporting period and cumulatively.

h) Report of number, length, and reasons for shipment delays to patients.

i) Summary of issues and complaints received by the Natpara REMS Program coordinating center; summary of resolution of the issues and complaints.

2. Knowledge, Attitudes, and Behavior (KAB) Survey Metrics: Prescribers
   a) Evaluation of prescribers'
      i. knowledge of indication for Natpara and limitations of use (appropriate patient selection)
      ii. knowledge of the potential risk for osteosarcoma associated to Natpara
      iii. knowledge of Natpara REMS Program requirements
      iv. awareness of Natpara REMS materials
      v. sources of knowledge about appropriate patient selection, the risks associated with Natpara, and REMS program requirements. Results will be stratified by type of prescriber (e.g., endocrinologists, internists, pediatricians, physician assistants, nurse practitioners, surgeons).

3. Knowledge, Attitudes, and Behavior (KAB) Survey Metrics: Patients
   a) Evaluation of patients'
      i. knowledge of indication for Natpara and limitations of use (appropriate patient selection)
      ii. knowledge of the potential risk for osteosarcoma associated to Natpara
      iii. knowledge of Natpara REMS Program requirements
      iv. awareness of relevant Natpara REMS Program materials (i.e., *Natpara Patient Brochure* and *Natpara REMS Patient-PrescriberAcknowledgment Form*).

4. 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 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) of the FDCA. 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 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:

BLA 125511 REMS ASSESSMENT METHODOLOGY

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:

BLA 125511 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR BLA 125511/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 125511/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 125511/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125511/ S-000
REMS ASSESSMENT
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 BLA 125511

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, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

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(s) 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.

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 Prescribing Information to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[1]

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[2] Information and Instructions for completing the form can be found at FDA.gov.[3] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[4]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Meghna M. Jairath, Pharm.D., Regulatory Project Manager, at (301) 796-4267.

Sincerely,

{See appended electronic signature page}

Anil Rajpal, M.D., M.P.H.
Deputy Director for Safety (Acting)
Division of General Endocrinology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURES: REMS

[2] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[3] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[4] https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-prescription-drug-promotion-opdp

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANIL K RAJPAL
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