BLA 761079/S-005,006,007

SUPPLEMENTS APPROVAL

BioMarin Pharmaceutical
Attn: Paul Pisacane
Director Regulatory Affairs
105 Digital Drive
Novato, CA 94949

Dear Mr. Pisacane:

Please refer to your supplemental biologics license applications (sBLAs) dated December 5, 2019, received December 6, 2019, and submitted under section 351(a) of the Public Health Service Act for Palynziq (pegvaliase-pqpz) injection.

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment received December 6, 2019.

These Prior Approval supplemental biologics applications provide for the following:

- S-005 proposes the inclusion of long-term efficacy, safety, and immunogenicity data in the product labeling;
- S-006 proposes the removal from the product label of the 20% blood phenylalanine (Phe) reduction threshold as a dose-escalation criterion;
- S-007 proposes the inclusion of a 60 mg maximum daily maintenance dosage.

APPROVAL & LABELING

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide) and include the labeling changes proposed in any pending “Changes Being Effected” (CBE) supplements.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), 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 (which includes new salts and new fixed combinations), 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 this product for this indication has an orphan drug designation, the submitted applications are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Palynziq was originally approved on May 24, 2018 and the REMS has not been modified since that date. The REMS consists of Elements to Assure Safe Use, Implementation System, and Timetable to for Submission of Assessments of the REMS. Your proposed modifications to the REMS consist of:

- Updates to the REMS materials to align with prior approval supplements S-005, S-006, and S-007.
- Additional updates to the REMS materials including:
    - Updated logo

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

- Formatting changes to bring attention to the safety video
- Clarification of the pharmacy enrollment process
- Addition of Spanish language materials for prescribers, pharmacies, and patients

Your proposed modified REMS, submitted on October 1, 2020, amended and appended to this letter, is approved.

The Timetable for Submission of Assessments to the REMS remains the same as that approved on May 24, 2018.

There are no additional changes to the REMS Assessment Plan as described in our December 5, 2019 letter.

We remind you that you must submit to the Agency certification that the Spanish language materials are an accurate and identical translation of the English language materials within 10 days of the REMS approval. The Spanish language links on the video and website may not go live until the certification is submitted.

We remind you that in addition to the REMS Assessment submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a 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 the 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 761079 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 761079 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR BLA 761079/S-XXX
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761079/S-XXX
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761079/S-XXX
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT YYY

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 761079/S-XXX
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 761079

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft (MS) Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but MS 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.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

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,

[3] For the most recent version of a guidance, check the FDA guidance web page athttps://www.fda.gov/media/128163/download.

accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

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, contact Nicolas Kong, Regulatory Project Manager at Nicolas.Kong@fda.hhs.gov or 240-402-0269.

Sincerely,

{See appended electronic signature page}

Patroula Smpokou, M.D.
Deputy Director (Acting)
Division of Rare Diseases and Medical Genetics (DRDMG)
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert or Medication Guide
  - Instructions for Use
- REMS

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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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/

PATROULA I SMPOKOU
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