BLA 761079/S-031

CORRECTED SUPPLEMENT APPROVAL

BioMarin Pharmaceutical Inc.
Attention: Audrey Harrison, MS
Director, Regulatory Affairs
105 Digital Drive
Novato, CA 94949

Dear Audrey Harrison:

Please refer to your supplemental biologics license application (sBLA) received August 28, 2025, and your amendments, submitted under section 351(a) of the Public Health Service Act for Palynziq (pegvaliase-pqpz) injection.

We also refer to our approval/complete response letter dated February 27, 2026, which contained the following error: The Medication Guide was erroneously included in the list of REMS elements.

This corrected action letter incorporates the correction of the error. The effective action date will remain February 27, 2026, the date of the original letter.

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated August 28, 2025.

This Prior Approval sBLA application provides for the expansion of the labeling to include pediatric patients with phenylketonuria (PKU) ages 12 to under 18 years and modifications to the approved Palynziq REMS.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is 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,

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

Instructions for Use, and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

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

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of hyperammonemia.

[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.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of hyperammonemia.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trial:

4958-1 Conduct a clinical trial to evaluate the effect of Palynziq (pegvaliase-pqpz) on ammonia levels in patients with phenylketonuria.

The timetable you submitted on February 19, 2026, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	02/2027
Trial Completion:	08/2028
Final Report Submission:	05/2029

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit clinical protocol(s) to your IND 076269 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o) , REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o), REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 601.70 to satisfy the periodic reporting requirement under section

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Palynziq was originally approved on May 24, 2018, and the most recent REMS modification was approved on December 9, 2023. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modifications to the REMS consist of:

- Modifying REMS materials to incorporate the proposed expansion of the patient population to include pediatric patients 12 to under 18 years of age.

- Modifying REMS requirements and materials to allow for the use of non-injectable forms of epinephrine.

Your proposed modified REMS, submitted on November 25, 2025, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on December 9, 2023.

The revised REMS Assessment Plan must include, but is not limited to, the following:

For each metric, provide the previous, current, and cumulatively reporting periods (where applicable) unless otherwise noted.

REMS Implementation and Operations

1. Post-Training Prescriber Knowledge Assessments (KA)

    a. Number of completed post-training KA for healthcare providers including methods of completion and number of attempts to complete

2. Palynziq REMS Enrollment Statistics

    a. Healthcare Providers

i. Number of newly enrolled and active (have prescribed Palynziq at least once during the reporting period) prescribers with profession (physician, advance practice nurse, physician assistant, etc.) and specialty

b. Pharmacies/Distributors

i. Number of newly enrolled and active (existing/dispensed a shipment of Palynziq) distributors/certified pharmacies with pharmacy type

c. Patients

i. Number of newly enrolled and active (have received at least one shipment of Palynziq during the reporting period) patients with demographics (age and gender)

d. The number of patients/healthcare providers/pharmacies/distributors that were de-enrolled and the reason for de-enrollment

3. Palynziq Utilization Data

a. Number of Palynziq prescriptions (new and refills) dispensed stratified by:

i. Pharmacy type

ii. Healthcare provider specialty

iii. Patient demographics (age and gender)

4. REMS Infrastructure and Performance

a. Palynziq REMS Call Center Report

i. Number of contacts by participant type (patient, healthcare provider, pharmacy, distributor, other)

1. For contacts related to REMS complaints, identify the participant, the complaint made and whether it relates to burden related to the REMS as designed or a problem with how the REMS is functioning.

2. For contacts related to adverse events associated with anaphylaxis or the treatment of anaphylaxis, identify the participant and a description of the adverse event, treatment, and outcome.

ii. Summary of frequently asked questions (FAQs) by participant type

iii. A summary report of corrective actions resulting from issues identified

5. REMS performance/compliance

a. Audits: Summary of audit activities conducted during the reporting period including but not limited to:

i. BioMarin's audit plan (beginning with the 36-month report, annually through the 60-month report, every 2 years in the 84-month report, and every 2 years thereafter)

ii. The number of audits performed

iii. A summary report of the processes and procedures that are implemented in order to be in compliance with the Palynziq REMS requirements

iv. A summary report of deviations found, associated corrective and preventive actions (CAPA) plans, and the status of CAPA plans

v. A copy of your REMS audit plan for pharmacies and wholesalers-distributors as an appendix with each assessment report

b. BioMarin's Compliance Plan (beginning with the 36-month report, annually through the 60-month report, every 2 years in the 84-month report, and every 2 years thereafter)

i. Number of prescribers, pharmacies, and distributors de-certified and reasons for decertification and actions to address non-compliance

ii. Number of Palynziq prescriptions dispensed that were written by non-certified prescribers and any action taken and outcome of action (e.g., provision of educational materials, prescriber became certified)

iii. Number of Palynziq prescriptions dispensed by non-certified pharmacies and the actions taken to prevent future occurrences

iv. Number of Palynziq prescriptions dispensed to de-enrolled or non-enrolled patients, sources of report, and actions taken to prevent future occurrences

v. Number of patients who received Palynziq without access to epinephrine

vi. Number of times a Palynziq prescription was dispensed because a certified pharmacy bypassed REMS authorization processes, to include a description of how the events were identified and any corrective actions taken

vii. Number of shipments sent to non-certified pharmacies, sources of the reports, and actions taken to prevent future occurrences

viii. Summary of any additional non-compliance, source of report, and resulting corrective and preventive actions (CAPA)

ix. A copy of your REMS noncompliance plan as an appendix with each assessment report including the criteria for noncompliance for REMS prescribers, outpatient specialty pharmacies, and specialty distributors, actions taken to address noncompliance for each case, and which events lead to de-certification from the REMS

c. Compliance with the REMS dispensing requirements for certified prescribers, certified pharmacies, and enrolled patients (beginning with the 48-month report, annually through the 60-month report, every 2 years in the 84-month report, and every 2 years thereafter).

i. The certified prescriber non-compliance is reviewed on a 12-month rolling calendar basis:

1. Errors in dispensing of prescriptions written by any non-certified prescriber (numerator) divided by the total number of prescriptions dispensed for the Palynziq REMS overall (denominator)

ii. The certified pharmacy non-compliance is reviewed on a 12-month rolling calendar basis:

1. Errors in dispense of prescriptions from any non-certified pharmacy (numerator) divided by the total number of prescriptions dispensed for the Palynziq REMS overall (denominator)

iii. The enrolled patient non-compliance is reviewed on a 12-month rolling calendar basis:

1. Errors in dispensing of prescriptions to any non-enrolled patient (numerator) divided by the total number of prescriptions dispensed for the Palynziq REMS overall (denominator)

d. Pharmacy adherence to ensuring that patients have access to or receive (non-expired) epinephrine when Palynziq is dispensed (beginning with the 48-month report, annually through the 60-month report, every 2 years in the 84-month report, and every 2 years thereafter)

   i. The certified pharmacy epinephrine non-compliance is reviewed on a 12-month rolling calendar basis:

      1. Number of Palynziq prescriptions dispensed from any pharmacy without documentation that the patient had a non-expired epinephrine (numerator), divided by the total number of Palynziq prescriptions dispensed for the Palynziq REMS overall (denominator)

e. The number of healthcare providers contacted by the REMS Call Center for not adhering to prescribing epinephrine with Palynziq from any sources (i.e., Request for Additional Information Regarding a Report associated with a Subcutaneous Injection, other)

   i. Include the REMS ID number for healthcare providers contacted

   ii. Provide as a ratio using the above as the numerator and the number of active prescribers in the Palynziq REMS as the denominator

Health Outcomes and/or Surrogates of Health Outcomes

6. Safety Surveillance

   a. Adverse event assessments of anaphylaxis

      i. Include the search strategy used to identify cases (via safety database) and specific MedDRA terms used to identify cases of interest

      ii. Include a line listing of all cases that includes: manufacturer control number, narrative, and assessment of causality

iii. Describe the process used to deduplicate case reports of anaphylaxis associated with Palynziq

iv. Verify REMS Identifications (IDs) for all patients enrolled in the REMS and confirm valid REMS IDs for all anaphylaxis case reports in the REMS, where enough information is available

v. Provide new safety findings to inform the incidence, severity, and frequency of anaphylaxis, and an assessment of the effectiveness of the REMS strategy in mitigating the risk

Safe Use Behaviors

7. Conduct a Retrospective Database Linkage Analysis: REMS Exposure Adjusted Incidence Rate of Anaphylaxis in Palynziq treated Patients (current reporting period and cumulatively)

Knowledge

8. Evaluation of Knowledge (conducted every 2 years with results submitted in each assessment report)

    a. Patient understanding of:

        i. How to recognize and respond to signs and symptoms of anaphylaxis

        ii. The need to carry epinephrine with them at all times

    b. Healthcare provider understanding of:

        i. The risk of anaphylaxis

        ii. The need to counsel patients about the risk of anaphylaxis and how to recognize and respond to signs and symptoms of anaphylaxis

        iii. The need to enroll patients in the Palynziq REMS

        iv. The need to prescribe epinephrine with Palynziq

Overall Assessment of REMS

9. 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.

Additionally, we recommend that you submit your protocol for the knowledge survey(s) for FDA review within 90 days of this letter. Prominently identify the submission containing the assessment instruments and methodology with the following wording in

bold capital letters, at the top of your cover letter and at the top of the first page of the main submission document: "**REQUEST FOR REMS ASSESSMENT METHODOLOGY PROTOCOL REVIEW/ SURVEY METHODOLOGIES**."

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 761079 REMS ASSESSMENT METHODOLOGY**
> **(**insert concise description of content in bold capital letters, e.g.,
> **ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)**

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

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-000**
> **CHANGES BEING EFFECTED IN 30 DAYS**
> **PROPOSED MINOR REMS MODIFICATION**
>
> ***or***
>
> **NEW SUPPLEMENT FOR BLA 761079/S-000**
> **PRIOR APPROVAL SUPPLEMENT**
> **PROPOSED MAJOR REMS MODIFICATION**

or

NEW SUPPLEMENT FOR BLA 761079/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 761079/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 761079

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

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling.*

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.[4]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 601.12(f)(4)]. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

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-related information [21 CFR 601.12(f)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(f)(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).

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, contact Diego Diaz, Regulatory Project Manager, via email at Diego.Diaz@fda.hhs.gov or at (301) 796-7182.

Sincerely,

{See appended electronic signature page}

Yuliya Yasinskaya, M.D.
Deputy Director
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
  - Medication Guide
  - Instructions for Use
- REMS

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/

YULIYA I YASINSKAYA
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