CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761079Orig1s000

Trade Name:	PALYNZIQ injection, 2.5 mg/0.5 mL, 10 mg/0.5 mL, and 20 mg/mL.
Generic or Proper Name:	pegvaliase-pqpz)
Sponsor:	BioMarin Pharmaceutical Inc.
Approval Date:	May 24, 2018
Indication:	To reduce blood phenylalanine concentrations in adult patients with phenylketonuria (PKU) who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management.

CENTER FOR DRUG EVALUATION AND RESEARCH

761079Orig1s000

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	**X**
Officer/Employee List	**X**
Multidiscipline Review(s) • **Summary Review** • **Office Director** • **Cross Discipline Team Leader** • **Clinical** • **Non-Clinical** • **Statistical** • **Clinical Pharmacology**	**X**
Product Quality Review(s)	**X**
Clinical Microbiology / Virology Review(s)	
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	**X**
Proprietary Name Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761079Orig1s000

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761079

BLA APPROVAL

BioMarin Pharmaceutical Inc.
Attention: Rishabh Jain
Senior Manager, Regulatory Affairs
105 Digital Drive
Novato, CA 94949

Dear Mr. Jain:

Please refer to your Biologics License Application (BLA), dated and received on June 30, 2017 (eCTD SN0001), and your amendments, submitted under section 351(a) of the Public Health Service Act (PHS Act) for PALYNZIQ (pegvaliase-pqpz) injection, 2.5 mg/0.5 mL, 10 mg/0.5 mL, and 20 mg/mL.

We additionally acknowledge receipt of your major amendment dated December 15, 2017 (eCTD SN0035), which extended the goal date by three months.

LICENSING

We have approved your BLA for Palynziq (pegvaliase-pqpz) effective on the date of this letter. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Palynziq under your existing Department of Health and Human Services U.S. License No. 1649. Palynziq is indicated to reduce blood phenylalanine concentrations in adult patients with phenylketonuria (PKU) who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture pegvaliase-pqpz drug substance at BioMarin Pharmaceutical Inc. in Novato, California. The final formulated drug product will be manufactured, filled, labeled, and packaged at Cook Pharmica, LLC in Bloomington, Indiana. You may label your product with the proprietary name, Palynziq, and market it in 2.5 mg/0.5 mL, 10 mg/0.5 mL, and 20 mg/mL single-dose prefilled syringes.

DATING PERIOD

The dating period for Palynziq shall be 24 months from the date of manufacture when stored at 5 ± 3 °C and protected from light. The date of manufacture shall be defined as the date of final

sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C or (b) (4) months from the date of manufacture when stored at less than or equal to (b) (4) °C. We have approved the stability protocol in your license application for the purpose of extending the expiration dating period of your drug substance under 21 CFR 601.12.

The dating period for your recombinant phenylalanine ammonia lyase (rAvPAL) intermediate shall be (b) (4) from the date of manufacture when stored at (b) (4) °C or (b) (4) months from the date of manufacture when stored at less than or equal to (b) (4) °C. Results of ongoing stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Palynziq to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to the release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Palynziq, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is 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, 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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide). 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*, located at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

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

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels that were submitted and received on February 23, 2018 (eCTD SN0050), as soon as they are available, but no later than 30 days after they are printed. Please submit these labels electronically according to the Guidance for Industry titled, *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*, located at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved BLA 761079**." Approval of this submission by FDA is not required before the labeling is used.

MARKET PACKAGE

Please submit one market package of the product, when it is available, to the following address:

Benjamin Vali
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room 5245
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** *if shipping via United States Postal Service (USPS).*
Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

ADVISORY COMMITTEE

Your application for Palynziq was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

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 drug product for this indication has an orphan drug designation, 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 known serious risk of severe immune-mediated adverse reactions including anaphylaxis, or identify an unexpected serious risk of embryofetal malformations in patients treated with Palynziq (pegvaliase-pqpz) injection. Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

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

3349-1 Prospective, longitudinal, observational study to assess long-term risks of severe immune-mediated adverse reactions in adult patients with phenylketonuria (PKU) treated with Palynziq (pegvaliase-pqpz). Each patient will be treated with Palynziq (pegvaliase-pqpz) over a minimum of 10 years. Evaluate the incidence rates of severe immune-mediated adverse reactions (including, but not limited to, hypersensitivity reactions, anaphylaxis, generalized skin reactions, and arthralgias), and collect information, including a full description of clinical features of the adverse reactions, to investigate associations and temporal relationships between the incidence and severity of all immune-mediated adverse reactions and other potential associated risk factors. Evaluate immunologic and inflammatory responses (immunologic testing, inflammatory markers), their effects on major organ function (e.g., kidney function), and immune-mediated effects on blood phenylalanine therapeutic response. Collect and analyze additional information, including, but not limited to, *PAH* genotype, dietary practices, and prior medical history. Specify concise case definitions, validation methods, and procedures for all study outcomes. An interim report will be submitted every two years during the conduct of the study.

The timetable you submitted on May 22, 2018 (eCTD SN0079) states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2018
Final Protocol Submission:	06/2019
Interim Report:	06/2021
Interim Report:	06/2023
Interim Report:	06/2025
Interim Report:	06/2027
Interim Report:	06/2029
Study Completion:	12/2029
Final Report Submission:	06/2030

3349-2 Prospective, observational study to assess the risks of pregnancy complications and adverse effects on the developing fetus and newborn (including, but not limited to, fetal malformations and pre-natal and post-natal growth restriction) from Palynziq (pegvaliase-pqpz) treatment during pregnancy. The study will collect and analyze data on blood phenylalanine concentrations during pregnancy in treated pregnant women with PKU and examine associations between Palynziq (pegvaliase-pqpz) treatment, blood phenylalanine concentrations, and adverse outcomes in the pregnant women and their offspring (fetus/newborn). The study duration will be a minimum of 10 years. An interim report will be submitted every two years during the conduct of the study.

The timetable you submitted on May 22, 2018 (eCTD SN0079) states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2018
Final Protocol Submission:	02/2019
Interim Report:	02/2021
Interim Report:	02/2023
Interim Report:	02/2025
Interim Report:	02/2027
Interim Report:	02/2029
Study Completion:	09/2029
Final Report Submission:	06/2030

3349-3 Pre-/Postnatal development study in rats treated with pegvaliase-pqpz using a set of testing methods that is sufficient to evaluate postnatal development, including the evaluation of physical developmental parameters and tests for effects on behavior, motor activity, sensory or sensorimotor functions, and reflex development.

The timetable you submitted on May 22, 2018 (eCTD SN0079) states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2018
Final Protocol Submission:	02/2019
Study Completion:	02/2020
Final Report Submission:	11/2020

3349-4 A study in pregnant rabbits to investigate the potential involvement of maternal phenylalanine depletion in fetal malformations.

The timetable you submitted on May 22, 2018 (eCTD SN0079) states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2020
Final Protocol Submission:	05/2021
Study Completion:	03/2022
Final Report Submission:	12/2022

3349-5 Revise the anti-PEG IgM anti-drug antibody assay in order to improve the drug tolerance and re-validate the assay.

The timetable you submitted on May 22, 2018 (eCTD SN0079) states that you will conduct this study according to the following schedule:

Study Completion:	10/2019
Final Report Submission:	12/2019

3349-6 Revise the anti-PEG IgG anti-drug antibody assay in order to improve the drug tolerance and re-validate the assay.

The timetable you submitted on May 22, 2018 (eCTD SN0079) states that you will conduct this study according to the following schedule:

Study Completion:	10/2019
Final Report Submission:	12/2019

3349-7 Re-evaluate anti-PEG IgM and IgG antidrug antibodies (ADA) in clinical samples from the phase 3 studies 165-301 and 165-302 using the anti-PEG IgM and IgG ADA assays with improved drug tolerance. Re-assess the impact of anti-PEG IgM and IgG ADA on pharmacokinetics (PK), efficacy, and safety.

The timetable you submitted on May 22, 2018 (eCTD SN0079) states that you will conduct this study according to the following schedule:

Study Completion:	06/2021
Final Report Submission:	12/2021

3349-8 Evaluate anti-PEG IgM and IgG ADA in samples from the observational study (according to postmarketing study 3349-1) using the anti-PEG IgM and IgG ADA assays with improved drug tolerance. Assess the impact of anti-PEG IgM and IgG ADA on efficacy and safety. An interim report will be submitted every two years during the conduct of the study.

The timetable you submitted on May 22, 2018 (eCTD SN0079) states that you will conduct this study according to the following schedule:

Interim Report:	06/2021
Interim Report:	06/2023
Interim Report:	06/2025
Interim Report:	06/2027
Interim Report:	06/2029
Study Completion:	12/2029
Final Report Submission:	06/2030

3349-9 Evaluate the sensitivity of the anti-pegvaliase-pqpz IgE ImmunoCAP assay to detect anti-PEG IgE antibodies, and make modifications to the method as needed. Test samples from treated patients with the current or modified assay in the prospective study (according to postmarketing study 3349-1) who experience anaphylaxis episodes in order to more comprehensively examine the underlying mechanism of the anaphylaxis. An interim report will be submitted every two years during the conduct of the study.

The timetable you submitted on May 22, 2018 (eCTD SN0079) states that you will conduct this study according to the following schedule:

Assay Methods Report:	10/2019
Interim Report:	06/2021
Interim Report:	06/2023
Interim Report:	06/2025
Interim Report:	06/2027
Interim Report:	06/2029
Study Completion:	12/2029
Final Report Submission:	06/2030

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of severe immune-mediated adverse reactions due to high antibody responses.

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

3349-10 Clinical trial of an appropriate immune tolerance induction (ITI) regimen to evaluate the ability of the ITI regimen (given prior to or concurrently with

Palynziq (pegvaliase-pqpz) treatment) to suppress immune responses, to reduce the risks of immune-mediated adverse reactions, and to enable improved therapeutic responses in adult patients with PKU treated with Palynziq (pegvaliase-pqpz).

The timetable you submitted on May 22, 2018 (eCTD SN0079), states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	12/2019
Final Protocol Submission:	06/2020
Trial Completion:	06/2025
Final Report Submission:	12/2025

Submit all protocols to your IND 076269, with a cross-reference letter to this BLA. Submit all postmarketing final reports to this 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).**

Submission of the protocols for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR 312 or FDA's regulations under 21 CFR 50 (Protection of Human Subjects) and 21 CFR 56 (Institutional Review Boards).

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 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 and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 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.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3349-11 Re-develop the enzyme kinetic assay (Km and kcat) so that the substrate concentration is held essentially constant (b) (4)

(b) (4) during the measurements of initial velocities. Re-validate the assay and re-evaluate the acceptance criteria for drug substance (DS) and drug product (DP) release and stability testing based on the re-validated assay.

The timetable you submitted on May 22, 2018 (eCTD SN0079) states that you will conduct this study according to the following schedule:

Study Completion: 12/2018
Final Report Submission: 01/2019

3349-12 Perform a study to evaluate the impact of the removal of kanamycin (b) (4) during the pegvaliase fermentation process. If the data support removal of kanamycin, then submit a plan for the removal of kanamycin from the pegvaliase manufacturing process.

The timetable you submitted on May 22, 2018 (eCTD SN0079) states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2019

3349-13 Evaluate product quality before and after shipping of formulated bulk drug (b) (4) The shipping study should demonstrate worst-case conditions regarding distance, duration, background temperature, and vibration.

The timetable you submitted on May 22, 2018 (eCTD SN0079) states that you will conduct this study according to the following schedule:

Study Completion: 12/2018
Final Report Submission: 03/2019

3349-14 Evaluate product quality before and after shipping of prefilled syringes (PFS). The shipping study should demonstrate worst-case conditions regarding distance, duration, background temperature, and vibration.

The timetable you submitted on May 22, 2018 (eCTD SN0079) states that you will conduct this study according to the following schedule:

Study Completion: 07/2018
Final Report Submission: 09/2018

3349-15 Implement [redacted] (b) (4) complete the process qualification report.

The timetable you submitted on May 22, 2018 (eCTD SN0079) states that you will conduct this study according to the following schedule:

Study Completion: 10/2018
Final Report Submission: 12/2018

Submit all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, and any changes in plans since the last annual report. 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 determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks. In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Palynziq (pegvaliase-pqpz) to ensure that the benefits of the drug outweigh the risk of anaphylaxis.

Your REMS must also include the following: elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Elements to assure safe use: Pursuant to 505-1(f)(1), we have determined that Palynziq (pegvaliase-pqpz) can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risk of anaphylaxis listed in the labeling of the drug. Your REMS includes the following elements to mitigate this risk:

- Healthcare providers have particular experience or training, or are specially certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions

Implementation System: The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above) that require pharmacies, practitioners, or health care settings that dispense the drug to be specially certified and that the drug be dispensed to patients with documentation of safe use conditions.

Your proposed REMS, submitted on May 22, 2018 (eCTD SN0079), amended and appended to this letter, is approved. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your REMS must be fully operational before you introduce Palynziq (pegvaliase-pqpz) into interstate commerce. The REMS assessment plan must include, but is not limited to, the following:

1. Palynziq REMS Implementation (6-month and 12-month assessment only)
    a. Product launch date
    b. Date when the Palynziq REMS website became active and is fully operational
    c. Date prescribers could become certified online, by mail, or by facsimile
    d. Date when the REMS call center is fully operational
    e. Number of unique visits to the Palynziq REMS website during the assessment period

2. Post-Training Prescriber Knowledge Assessments (KA) (6-month and 12-month assessment only)
    a. Number of completed post-training knowledge assessments for healthcare providers including methods of completion and number of attempts to complete
    b. Summary of the most frequently missed KA questions

3. Palynziq REMS Enrollment Statistics (per reporting period and cumulatively)
    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

4. Palynziq Utilization Data (per reporting period and cumulatively)
    a. Number of Palynziq prescriptions (new and refills) dispensed, stratified by:
        i. Pharmacy Type
        ii. Healthcare Provider specialty
        iii. Patient demographics (age and gender)

5. REMS Infrastructure and Performance (current reporting period and cumulatively)
    a. Palynziq REMS Call Center Report

i. Number of contacts by stakeholder type (patient, healthcare provider, pharmacy, distributor, other)
ii. Summary of frequently asked questions (FAQ) by stakeholder type
iii. A summary report of corrective actions resulting from issues identified

6. Safety Surveillance
    a. Adverse event assessments of anaphylaxis
        i. Include the search strategy used to identify cases (via safety database) and specific Medical Dictionary for Regulatory Activities (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
    b. A study to evaluate prescribers' adherence to the need to prescribe auto-injectable epinephrine with Palynziq

7. REMS Performance/Compliance
    1. Audits: Summary of audit activities conducted during the reporting period including, but not limited to:
        a. An overview of the audit plan for each stakeholder
        b. The number of audits performed
        c. A summary report of the processes and procedures that are implemented in order to be in compliance with the Palynziq REMS requirements
        d. A summary report of deviations found, associated corrective and preventive action (CAPA) plans, and the status of CAPA plans
    2. Number of prescribers and pharmacies and distributors de-certified, and the reasons for decertification, and actions to address non-compliance
    3. 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)
    4. Number of Palynziq prescriptions dispensed by noncertified pharmacies and the actions taken to prevent future occurrences
    5. Number of Palynziq prescriptions dispensed to de-enrolled or non-enrolled patients, sources of the reports, and actions taken to prevent future occurrences
    6. Number of patients who received Palynziq without access to auto-injectable epinephrine
    7. Number of times a Palynziq prescription was dispensed because a certified pharmacy bypassed REMS authorization processes, including a description of how the events were identified and any corrective actions taken
    8. Number of shipments sent to non-certified pharmacies, sources of the reports, and actions taken to prevent future occurrences
    9. Summary of any additional non-compliance, sources of the reports, and resulting CAPA plans

8. Evaluation of Knowledge (beginning with the 12-month assessment)
    a. Patient understanding of:
        i. How to recognize and respond to signs and symptoms of anaphylaxis
        ii. The need to carry auto-injectable 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 auto-injectable epinephrine with Palynziq

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). 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, proposed 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 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 a REMS modification,* 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 761079 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - 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

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

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 REVISION 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, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in MS Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in 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 eLIST.

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

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 package insert to:

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

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. 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.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involving a distributed product may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from

improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, contact Benjamin Vali, Regulatory Project Manager, at (301) 796-4261 or benjamin.vali@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling:
Prescribing Information (PI)
Medication Guide (MG)
Instructions for Use (IFU)
Carton and Container 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/

JULIE G BEITZ
05/24/2018