CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761079Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of New Drugs III
Division of Gastroenterology and Inborn Errors Products

BLA #s:	761079
Products:	**PALYNZIQ (pegvaliase-pqpz) injection, for subcutaneous use**
APPLICANT:	BioMarin Pharmaceutical, Inc.
FROM:	Joyce Korvick, M.D., M.P.H.
DATE:	May 24, 2018

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (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 [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultation between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use are necessary for PALYNZIQ (pegvaliase-pqpz) injection, for subcutaneous use to ensure that the benefits of the drug outweigh the risks of the serious outcomes of anaphylaxis. In reaching this determination, we considered the following:

A. PKU is a rare, autosomal recessive, inborn error of Phenylalanine (Phe) breakdown with an incidence in the U.S. of 1 in 10,000 – 15,000 live births[1].The number of adult patients in the United States with phenylketonuria (PKU) who have uncontrolled blood phenylalanine concentrations is difficult to estimate. Available therapeutic options include 1) a PKU specific diet consisting of lifetime restriction of dietary protein and Phe intake, and 2) Kuvan (sapropterin, synthetic tetrahydrobiopterin), which is indicated only for those patients with PKU who are "Kuvan responsive" (approximately 30% of all PKU patients). Of note, patients with classical (severe) PKU comprise a subgroup in which diet restrictions are the strictest and who are the least likely to respond to Kuvan. Thus, an unmet medical need exists for the majority of patients with PKU, and particularly for

[1] https://ghr nlm nih.gov/condition/Phenylketonuria#statistics

those patients with the classical form of the disease who are unable to adhere to the very strict restrictions of the PKU diet and in whom Kuvan is not a viable therapeutic option.

B. PKU is typically diagnosed shortly after birth via newborn screening detecting high Phe concentrations in blood. PKU presents a spectrum of disease severity ranging from partial enzyme deficiency (mild and moderate PKU) to complete enzyme deficiency (classical PKU). When untreated, patients with classical PKU typically present with blood Phe concentrations >1,200 μmol/L while those with mild or moderate PKU have blood Phe concentrations between 600 and 1,200 μmol/L. Without dietary intervention, patients with classical PKU (the most severe form) develop profound and irreversible intellectual disability. Early dietary intervention with protein and Phe intake restriction can prevent the profound intellectual disability. However, since the dietary interventions are poorly tolerated patients continue to experience suboptimal cognitive outcomes, behavioral and psychiatric disease, executive dysfunction, and impaired attention in their adult years. Clinical outcomes and symptom severity in adults with PKU depend on both current and historical blood Phe control. Clinical outcomes appear to be better when blood Phe is maintained below 600 μmol/L. Reduction in blood Phe concentration is the therapeutic goal in PKU management and life-long maintenance of blood Phe concentration below 600 μmol/L is a generally accepted treatment goal. Further blood Phe reductions below 360 μmol/L, when possible, are generally encouraged and recommended by the American College of Medical Genetics and Genomics[2]. Management guidelines during pregnancy recommend stricter blood Phe control in the range of 120-360 μmol/L.

C. Phenylketonuria (PKU) is a serious, rare, inherited disease which results in chronic neurologic, psychiatric, and functional disability when untreated or undertreated. Reduction in blood phenylalanine (Phe) concentrations is the overall therapeutic goal in the management of patients with PKU. Patients with the classical (severe) form of the disease exhibit higher blood Phe concentrations. Control of blood Phe concentrations within the generally recommended therapeutic range is particularly challenging for adults with PKU owing to the difficulty of adhering to strict daily protein and Phe intake requirements. Poor adherence to dietary management can result in adverse clinical outcomes from untreated or undertreated PKU including psychiatric disease, executive dysfunction, and attention and memory impairment.

The benefit of this product is to reduce the Phe concentration in blood. Statistically significant reductions in blood Phe concentrations from pre-treatment baseline were demonstrated in patients treated with pegvaliase at target doses of 20 mg once daily and 40 mg once daily. The magnitude of Phe reductions in clinical trials of pegvaliase are clinically important given that ACMG guidelines recommend goal Phe levels between 120-360 μmol/L, and that patients were also able to achieve Phe reductions on an unrestricted diet. Most patients achieved a therapeutic response (either a ≥ 20% blood Phe reduction from pre-treatment baseline or blood Phe concentration ≤ 600 μmol/L) within 4 weeks of treatment with 20 mg/day while up to 40 weeks of treatment was

[2] Vockley J, Andersson HC, Antshel KM et al. Phenylalanine hydroxylase deficiency: diagnosis and management guideline. *Genet Med*. 2014 Feb;16(2):188-200

needed in others to reach that response. In patients in whom therapeutic response was not achieved while on 20 mg/day for at least 24 to 32 consecutive weeks, some achieved therapeutic response when the dose was escalated to 40 mg/day for at least an additional 16 consecutive weeks. The degree of blood Phe reduction with pegvaliase treatment was variable among the treated patients and no single patient characteristic or immune parameter was found to be predictive of therapeutic response.

D. Palynziq will be used chronically to reduce the blood level of Phe in patients with PKU, a life-long disease. Patients who respond to therapy in the first 24 (b) (4) weeks with an appropriate decrease in blood phenylalanine concentrations, will remain on a continuous dose of 20 mg once daily. The dose may be increased to 40 mg daily depending on response and tolerability. Discontinuation for anaphylaxis and re-initiation of treatment after anaphylaxis may be considered.

E. The known serious adverse event of anaphylaxis with the use of Palynziq was seen in clinical trials. Twenty-six out of 285 (9%) patients experienced a total of 37 anaphylaxis episodes in clinical trials of Palynziq during induction/titration/maintenance dosing. The exposure-adjusted rate of anaphylaxis was highest during the induction and titration phases (0.15 episodes/person-years; 5% of patients with at least one episode) and decreased in the maintenance phase (0.04 episodes/person-years; 6% of patients with at least one episode). Signs and symptoms of anaphylaxis reported in clinical trials of Palynziq included syncope, hypotension, hypoxia, dyspnea, wheezing, chest discomfort/chest tightness, tachycardia, angioedema (swelling of face, lips, eyes, tongue), throat tightness, skin flushing, rash, urticaria, pruritus, and gastrointestinal symptoms (vomiting, nausea, diarrhea). In clinical trials of Palynziq, anaphylaxis generally occurred within 1 hour after injection (84%; 28/37 episodes); however, delayed episodes also occurred up to 48 hours after Palynziq administration. Most episodes of anaphylaxis occurred within the first year of dosing (78%, 29/37 episodes), but cases also occurred after one year of dosing and up to 834 days (2.3 years) into treatment. Management of anaphylaxis in Palynziq clinical trials included: administration of auto-injectable epinephrine (54%; 20/37 episodes), corticosteroids (54%; 20/37 episodes), antihistamines (51%; 19/37 episodes), and/or oxygen (5%; 2/37 episodes). Eighteen out of the 26 (69%) patients who experienced anaphylaxis were rechallenged with Palynziq and 5 out of the 18 patients who were rechallenged (28%) had recurrence of anaphylaxis. All anaphylaxis episodes resolved without sequelae.

   In addition to the risk of anaphylaxis, hypersensitivity reactions, have been reported in 196 out of 285 (69%) patients treated with Palynziq. The exposure adjusted rate of these hypersensitivity reactions was highest during the induction and titration phases (4.5 episodes/person-year; 50% of patients) and decreased in the maintenance phase (1.5 episodes/person-year; 57% of patients).

   There is uncertainty about the long-term clinical safety risks associated with chronic use of pegvaliase beyond the duration of the completed trials. Long-term clinical effects arising from the chronic, high-titer immune response to the PAL protein will need to be further assessed in the post-marketing setting over a longer duration of exposure and in a

larger patient population. The identified immunologic and inflammatory responses during pegvaliase treatment in the clinical trials (e.g., high-titer, sustained elevations in anti-drug antibodies, low complement C3 and C4 levels, high circulating immune complex levels, elevations in C-Reactive Protein and hs-CRP) should be further assessed in the context of potential long-term adverse effects and potential effects on therapeutic response. Moreover, given the relatively high PEG content of pegvaliase and the fact that the clinical effects of chronic PEG exposure in humans are currently unknown, potential adverse effects associated with long-term PEG exposure need to be further assessed in the post-marketing setting.

Embryofetal malformations (of the skeleton, kidneys, lungs, and eyes) and embryofetal toxicity (increased resorptions, reduced fetal weight) were observed in the offspring of pregnant rabbits treated with pegvaliase in the nonclinical program at a dosage which was 7.5 times higher than the maximum recommended daily dose; these adverse fetal effects in the rabbit study were associated with strong signs of maternal toxicity, including marked reductions in weight gain and food consumption, and death. While the significance of these findings for humans remains unknown, it requires further evaluation in the post-marketing setting and necessitates appropriate education of patients and prescribers when considering the use of pegvaliase during pregnancy. The prescribing information for pegvaliase recommends careful consideration of the benefits and risks of pegvaliase when continuing treatment during pregnancy including consideration of the known fetal risks of untreated or undertreated maternal PKU (intellectual disability, microcephaly, cardiac malformations). In addition, an additional study conducted in rabbits post-approval will further evaluate the effects of hypoPhenylalaninemia (and its role in the development of fetal malformations) on pregnant animals and their offspring. Moreover, a post-approval pregnancy surveillance program will be instituted to further evaluate safety risks associated with pegvaliase treatment in pregnant women with PKU and their offspring.

F. PALYNZIQ (pegvaliase-pqpz) injection, for subcutaneous use is a new molecular entity.

The REMS will include 1.) elements to assure safe use, including that prescribers must be certified with the program by enrolling in the program and completing training, prescribers must prescribe auto-injectable epinephrine with Palynziq, pharmacies must be certified with the program and must dispense only to patients who are enrolled and who have a prescription for auto-injectable epinephrine, documentation of safe use conditions including patients must enroll in the program and be educated about the risk of anaphylaxis by a certified prescriber to ensure they understand the risks and benefits of treatment with Palynziq, and patients must have auto-injectable epinephrine available at all times while taking Palynziq; 2.) an implementation system; 3.) a timetable for submission of assessments of the REMS.

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/s/

JOYCE A KORVICK
05/24/2018

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761079
PDUFA Goal Date	May 24, 2018
OSE RCM #	2017-1327, 2017-1329
Reviewer Name(s)	Laura Zendel, PharmD Anahita Tavakoli, MA
Team Leader	Donella Fitzgerald, PharmD
Deputy Division Director	Jamie Wilkins Parker, PharmD
Review Completion Date	May 24, 2018
Subject	Determination and Evaluation of the Proposed REMS for Palynziq
Established Name	Pegvaliase-pqpz
Trade Name	Palynziq
Name of Applicant	BioMarin
Therapeutic Class	PEGylated phenylalanine-metabolizing enzyme
Formulation(s)	2.5 mg/0.5 ml, 10 mg/0.5 ml, 20 mg/1 ml prefilled syringe
Dosing Regimen	The starting dosage is 2.5 mg by subcutaneous injection once per week for 4 weeks. The dosage should be escalated in a step-wise manner based on tolerability to achieve a dosage of 20 mg by subcutaneous injection daily. If a minimum of 20% blood phenylalanine reduction is not achieved after 24 on 20 mg/day, the dosage may be increased to 40 mg/day.

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Palynziq (pegvaliase-pqpz) is necessary to ensure the benefits outweigh its risks. BioMarin submitted a Biologics Licensing Application (BLA 761079) for pegvaliase-pqpz with the proposed indication to reduce blood phenylalanine (Phe) concentrations in adult patients with phenylketonuria (PKU) who have uncontrolled blood Phe levels > 600 µmol/L on existing management. The risk associated with pegvaliase-pqpz includes anaphylaxis. The Applicant submitted a proposed REMS which includes (b) (4) elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.

DRISK and DGIEP have determined that a REMS is required to ensure the benefits of pegvaliase-pqpz outweigh its risks. Pegvaliase-pqpz will provide effective therapy for the treatment of PKU, where there is serious unmet need in adult PKU patients who are unable to control their blood Phe levels on available existing therapy. However, due to the potentially life-threatening risk of anaphylaxis, risk mitigation measures beyond the approved labeling are necessary. Prescribers and patients must be made aware of the risk, and auto-injectable epinephrine must be prescribed to all patients receiving pegvaliase-pqpz, which should be available at all times during pegvaliase-pqpz treatment. A REMS will ensure that prescribers are aware of the risk, patients are appropriately counseled and trained on how to recognize and respond to signs and symptoms of anaphylaxis and ensure that patients carry auto-injectable epinephrine with them at all times while taking pegvaliase-pqpz.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Palynziq (pegvaliase-pqpz) is necessary to ensure its benefits outweigh its risks. BioMarin submitted Biologics Licensing Application (BLA) 761079 for Palynziq with the proposed indication to reduce blood phenylalanine (Phe) concentrations in adult patients with phenylketonuria (PKU) who have uncontrolled blood Phe levels > 600 µmol/L on existing management. This application is under review in the Division of Gastrointestinal and Inborn Errors Products (DGIEP). The Applicant's proposed REMS consists of (b) (4) elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of Palynziq outweigh the risks of serious outcomes of anaphylaxis. DRISK and DGIEP agree that a REMS with ETASU A (prescriber certification), B (pharmacy certification), and D (safe use conditions) is necessary for the benefits of Palynziq to outweigh its risks.

2 Background

2.1 PRODUCT INFORMATION

Palynziq (pegvaliase-pqpz), a new molecular entity[a], is a PEGylated phenylalanine-metabolizing enzyme proposed to reduce blood Phe concentrations in adult patients with PKU who have uncontrolled blood

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

Phe levels > 600 µmol/L on existing management. Palynziq is a phenylalanine ammonia lyase enzyme that converts Phe to ammonia and trans-cinnamic acid that are metabolized by the liver and excreted in the urine, respectively. It substitutes for the deficient phenylalanine hydroxylase (PAH) enzyme activity and reduces blood phenylalanine levels in the body.

Palynziq is proposed to be available as 2.5 mg/0.5 ml, 10 mg/0.5 ml, and 20 mg/1 ml prefilled syringes to be administered by subcutaneous route. The proposed initial induction dosage is 2.5 mg by subcutaneous injection once weekly for 4 weeks. The dosage should be titrated in a step-wise manner according to Table 1 based on tolerability to achieve a dosage of 20 mg by subcutaneous injection once daily. If a minimum of 20% blood phenylalanine reduction is not achieved after at least 24 weeks on 20 mg/day, the dosage may be increased to a maximum of 40 mg/day. Patients who do not achieve a response (at least a 20% reduction in blood Phe concentration from pre-treatment baseline or a blood phenylalanine concentration ≤ 600 µmol/L) after 16 weeks of continuous treatment with the maximum dosage of 40 mg once daily should discontinue Palynziq.[b]

Table 1: Proposed Dosage Titrating Regimen

Treatment	Palynziq Dosage[c]	Duration[d]
Induction	2.5 mg once weekly	4 weeks
Titration	2.5 mg twice weekly	1 week
	10 mg once weekly	1 week
	10 mg twice weekly	1 week
	10 mg four times a week	1 week
	10 mg once daily	1 week
Maintenance	20 mg once daily	24 weeks
Maximum	40 mg once daily	16 weeks[e]

Palynziq can be used for inpatient or outpatient use, however, the initial dose must be administered under the supervision of a healthcare provider equipped to manage anaphylaxis and patients must be

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[c] Individualize treatment to the lowest effective and tolerated dosage. Consider increasing to a maximum of 40 mg once daily in patients who have not achieved a response with 20 mg once daily continuous treatment for at least 24 (b) (4) weeks.

[d] Additional time may be required prior to each dose escalation based on patient tolerability

[e] Individualize treatment to the lowest effective and tolerated dosage. Consider increasing to a maximum of 40 mg once daily in patients who have not achieved a response with 20 mg once daily continuous treatment for at least 24 weeks

closely observed for at least 60 minutes following the injection. Prior to self-injection, healthcare providers should confirm patient competency with self-administration, ability to recognize signs and symptoms of anaphylaxis, and administer auto-injectable epinephrine, if needed. The patient will need to have access to auto-injectable epinephrine at all times while taking Palynziq. Prescribers should consider having an adult observer for patients who may need assistance in recognizing and managing anaphylaxis during Palynziq treatment. If an adult observer is needed, the observer should be present during and for at least 60 minutes after Palynziq administration, should be able to administer auto-injectable epinephrine, and call for emergency medical support. Prescribers can also consider premedication with a H_1-receptor antagonist, H_2-receptor antagonist, and/or antipyretic prior to Palynziq administration based upon individual patient tolerability. Further, risks and benefits of readministering Palynziq following an episode of anaphylaxis should be considered. If the decision is made to readminsiter Palynziq after an anaphylaxis episode, the first dose should be administered under the supervision of a healthcare provider equipped to manage anaphylaxis and closely observe the patient for at least 60 minutes following the dose, as outlined in the label. Subsequent titration should be based on patient tolerability and therapeutic response.

Palynziq was granted fast track designation and priority review. Palynziq is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761079 relevant to this review:

- 03/08/1995: Orphan Drug designation granted
- 11/22/2011: Fast Track designation granted
- 05/06/2014: Teleconference between the agency and BioMarin in response to the 15 day Safety Report filed April 20, 2014 in which there were three cases of severe anaphylaxis. The Agency had two primary safety concerns: patient safety during self-dosing at home and dosing subjects younger than 18 years of age. Strategies to mitigate the risk of anaphylaxis were discussed and implemented in all ongoing studies (PAL-003, 165-301, and 165-302) which included (b) (4) premedication, the presence of a responsible adult observer for 1 hour after dosing (b) (4) (b) (4), and training and education on how to recognize and respond to hypersensitivity reactions including anaphylaxis. BioMarin also agreed to suspend enrollment and dosing of subjects less than 18 years of age.[1,2]
- 11/14/2016: BioMarin sought comments for their proposed REMS with a communication plan for pegvaliase-pqpz submitted in a Type B pre-BLA Meeting Briefing Package.
- 12/09/2016: BioMarin was informed via preliminary comments in response to a pre-BLA meeting request that their proposed REMS, although described as a communication plan, actually consists of ETASU to address the risks of anaphylaxis and severe hypersensitivity reactions. The Applicant was encouraged to submit a proposed REMS with ETASU with the BLA application should they believe it to be required to ensure the benefits outweigh the risks.

- 06/30/2017: BLA 761079[3] submission for a PEGylated phenylalanine-metabolizing enzyme indicated to reduce blood phenylalanine in adult patients with phenylketonuria who have uncontrolled blood phenylalanine levels > 600 µmol/L on existing management received. The Applicant voluntarily submitted a REMS with the application and based the REMS requirements on the risk mitigation strategies implemented in the clinical trials.
- 7/31/2017: Information Request[4] (IR) sent to Applicant requesting further information on the trained observer, the duration of premedications, the pharmacy certification process and the pharmacy verification process.
- 8/10/2017: Applicant Orientation Meeting between the Applicant and the Agency via teleconference. The Applicant provided rationale for their REMS structure and elements and further details surrounding the concept of the trained observer and its feasibility in a real world setting. The Agency informed the Applicant that if it is determined that a REMS is necessary and pharmacy certification is required, they would need to develop a pharmacy certification form and provide pharmacy training materials.
- 8/29/2017: Priority review granted[5]
- 9/12/2017: 74-Day letter[6] sent to the Applicant that included IRs to gather more information on the role and training of the proposed "trained observer," the use of epinephrine, the outcomes before and after implementing "amendment 2" and when patients were determined to be eligible for self-injection at home.
- 10/31/2017: Meeting between the Agency and the National PKU Alliance. Patients and prescribers who participated in the clinical trials shared their experience with pegvaliase-pqpz.
- 11/1/2017: Safety Teleconference with BioMarin. The Applicant presented rationale for the trained observer, discrepancies in coding for anaphylaxis, reasons for study drug discontinuation, and rationale for data integration and pooling. The Applicant was not able to clarify what impact the individual interventions had on the anaphylaxis rate in clinical trials as they were all implemented simultaneously.
- 11/17/2017: Midcycle communication with the Applicant. The Applicant was informed that the Agency had not made a final decision about whether or not a REMS was needed.
- 12/13/2017: REMS Oversight Committee (ROC) Meeting. The ROC agreed that a REMS is necessary for pegvaliase-pqpz and the requirements should include prescriber certification, pharmacy certification and safe use conditions including patient counseling and access to auto-injectable epinephrine.
- 12/21/2017: Major amendment acknowledgment letter sent to the applicant; PDUFA goal date extended by 3 months.
- 1/31/2018: The Agency notified the Applicant via teleconference that the Agency agrees that a REMS will be necessary to ensure the benefits outweigh the risks of pegvaliase-pqpz. The Agency also informed the Applicant that (b) (4)

[redacted](b) (4) should be removed as part of the REMS and that a patient directed safety video, pharmacy enrollment form and program overview should be added to the REMS. Finally, the Applicant was informed that the addition of a registry to be included as a requirement in the REMS is still under discussion within the Agency.

- 2/23/2018: Preliminary comments on the REMS document, supporting document, and appended materials were sent to the Applicant.
- 3/9/2018: REMS correspondence received by the Agency which included the REMS document, REMS supporting document, and all appended materials including Pharmacy Enrollment Form, Program Overview, Prescriber Knowledge Assessment, and Safety Video Transcript.
- 3/15/2018: REMS Amendment received by the Agency that included the .PDF layouts of the REMS materials.
- 4/5/2018: REMS correspondence received by the Agency that included the patient safety video storyboard.
- 4/16/2018: Comments on the REMS document, supporting document, and appended materials were sent via email to the Applicant.
- 4/23/2018: REMS correspondence received by the Agency which included the REMS document, supporting document, and REMS appended materials. Two of the materials were mis-labeled and therefore missing from the submission. The Agency emailed the Applicant to make them aware and ask them to resubmit the missing materials.
- 4/24/2018: Missing REMS materials were submitted by the Applicant.
- 5/7/2018: REMS Amendment received by the Agency that included updates to REMS materials to align with labeling changes.
- 5/10/2018: The Agency sent an IR to the Applicant to clarify how closed systems (Kaiser, VA, DOD, etc.) will be incorporated into the REMS. The Applicant responded that they will include this information in the next REMS Amendment.
- 5/11/2018: Comments on the REMS document, supporting document and appended materials were sent via email to the Applicant. The majority of comments were editorial in nature to align with labeling.
- 5/15/2018: REMS Amendment received by the Agency.
- 5/16/2018: Comments on the supporting document and appended materials were sent via email to the Applicant to align the pdf layout materials with the word version.
- 5/18/2018: REMS Amendment received by the Agency.
- 5/21/2018: Comments on the REMS document, supporting document, and appended materials were sent via email to the Applicant to fix minor typographical errors and align the Safety Video with the Patient Guide.

- 5/22/2018: REMS Amendment received by the Agency.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition[7]

Phenylketonuria (PKU) is a rare, serious, autosomal recessive genetic metabolic disorder characterized by a deficiency of phenylalanine hydroxylase (PAH), which converts Phe to tyrosine. As a result, Phe accumulates to abnormally high levels in the blood and becomes toxic to the brain. Clinical manifestations in untreated patients include intellectual disability, developmental delay, behavioral and emotional problems, hyperactivity, poor bone strength, musty odor, microcephaly and poor quality of life.[f] PKU is estimated to occur in 1 in 10,000-15,000 newborns in the United States and is considered an orphan disease.[g] PKU is the first inborn error of metabolism to be included in universal newborn screening in the United States. As such, the disease is often diagnosed shortly after birth. Early identification of PKU with newborn metabolic screening and early treatment with Phe-restricted diets significantly improved cognitive outcomes in children.

Adult PKU patients often have untreated blood Phe levels > 1,200 µmol/L.[8] Uncontrolled blood Phe in adulthood is associated with impairment of neuropsychiatric, neurocognitive and executive function, a heterogeneous variety of behavioral and psychiatric problems, including depression and anxiety, and negatively affects patient quality of life. High blood Phe levels also negatively affects mood and ability to sustain attention.[9] Elevated maternal serum Phe concentration during early pregnancy is teratogenic and may result in Phe embryopathy. Embryopathic effects of elevated Phe levels during pregnancy in maternal PKU include growth retardation, microcephaly, psychomotor retardation, and congenital heart defects.[10]

3.2 Description of Current Treatment Options

PKU patients require lifelong stringent Phe restriction. American College of Medical Genetics and Genomics (ACMG) practice guidelines recommend lifelong management of PKU, with a goal of maintaining blood Phe concentrations in the range of 120-360 µmol/L.[11] Management involves strict dietary restriction of Phe and the use of medical foods that include protein substitutes without Phe. Compliance with a Phe restricted diet can be difficult due to limited choices, poor palatability of medical foods, intense effort and time to calculate protein intake, and psychosocial issues surrounding eating with such restrictions.

[f] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug*

[g] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved*

Kuvan (sapropterin dihydrochloride) was granted full approval in the US in December 13, 2007 for the reduction of blood Phe levels in adults and children with hyperphenylalaninemia due to tetrahydrobiopterin (BH4)-responsive PKU in conjunction with restricted Phe intake. The recommended starting dose is 10-20 mg/kg taken one daily by mouth with a meal. Doses of sapropterin may be adjusted in the range of 5-20 mg/kg. Sapropterin is available as 100 mg tablets and as 100 mg and 500 mg powder for oral solution. Hypersensitivity reactions including anaphylaxis have occurred with sapropterin. Additionally, patients should be monitored for gastritis, liver function in patients with liver impairment, folate levels with medications known to inhibit folate metabolism or with levodopa, hypotension when given with medications known to affect nitric oxide-mediated vasorelaxation, and hyperactivity. Patients with PKU have varying responsiveness to sapropterin, with patients with residual PAH enzyme activity being more likely to benefit. Patients with limited or no PAH enzyme function may not see any benefit from sapropterin.

4 Benefit Assessment

Evidence of the effectiveness of pegvaliase-pqpz for the treatment of adult patients with uncontrolled blood Phe was derived from two pivotal Phase 3 trials (165-301 and 165-302). Subjects 18 years of age and older with PKU and a current blood Phe > 600 µmol/L were eligible for enrollment. Subjects had to be willing and able to maintain a consistent intact protein intake and medical food protein intake and maintain stable doses of any medications used for attention deficit hyperactivity disorder, depression or other psychiatric disorder.

165-301 (NCT01819727) was an open-label, randomized, multi-center study of adults with PKU to assess safety and tolerability of self-administered pegvaliase-pqpz in an induction/titration/maintenance regimen with a target maintenance dose of 20 mg or 40 mg. At study enrollment, all patients demonstrated inadequate blood Phe control on existing management. Existing management options included prior or current restriction of dietary Phe and protein intake, and/or prior treatment with sapropterin. The primary objectives were safety and tolerability of pegvaliase-pqpz, and the secondary objective was change in blood Phe concentration.

165-302 (NCT02468570, PRISM303)) was a four-part study. In Part 1, pegvaliase-pqpz treated subjects from Study 301 or Phase 2 Study (PAL-003, NCT00924703) remained on 20 mg/day or 40 mg/day for up to 13 weeks to reach $\geq$ 20% blood Phe reduction. Those that achieved $\geq$ 20% blood Phe reduction could participate in Part 2, a randomized, double-blind, placebo-controlled, discontinuation study. Subjects were eligible for Part 2 if they had $\geq$ 20% blood Phe reduction from naïve baseline levels. Subjects were randomized 1:2 to placebo or maintain current dose of 20 mg or 40 mg for treatment duration of 8 weeks in Part 2. Part 3 was a pharmacokinetic analysis of 20 mg/day and 40 mg/day dosages. Subjects from Part 1 who were not eligible to participate in Part 2 and subjects who completed Parts 2 and 3 could participate in Part 4. Part 4 was an open label extension which included dose regimens of 10 mg/day, 20 mg/day, 40 mg/day and 60 mg/day if after 8 weeks of dosing at 40 mg/day the investigator determined an increase in dose was necessary based on patient response. The primary endpoint was change in blood Phe concentration from Part 2 baseline to Part 2 Week 8. Secondary endpoints included

inattention and mood, and changes from Part 2 baseline to Part 2 Week 8 in neurocognitive and neuropsychiatric symptom scores[h].

Safety data was also included from Phase 1 study (PAL-001, NCT00634660) and Phase 2 studies (PAL-002, NCT00925054, PAL-004, NCT01212744, 165-205, NCT1560286, PAL-003).

Results of 165-301

A total of 261 subjects participated in Study 301, 131 subjects were randomized to 20 mg and 130 subjects were randomized to 40 mg. Mean blood Phe concentration at baseline was 1241.0 (range 285-2186) in the 20 mg group and 1224.4 (range 483-2330) in the 40 mg group. Of the 261 enrolled patients, 195 (75%) patients reached their randomized dosage. Among the patients who reached their randomized dosage, 103 out of 131 (79%) patients reached maintenance dosage of 20 mg with a median time of 10 weeks (range 9 to 29 weeks) and 92 out of 130 patients (71%) reached maintenance dosage of 40 mg with a median time of 11 weeks (range 10 to 33 weeks). At week 36, mean blood Phe was 868.4 (range 0-1738) in the 20 mg group and 624.4 (range 0-1606) in the 40 mg group. It should be noted that the sample size declined over time as subjects discontinued early or were transitioned early to Study 302. Of the 261 patients who enrolled in Study 301, 152 patients continued to the eligibility period of Study 302, 54 patients discontinued treatment, 4 patients completed Study 301 and did not continue on to Study 302, and 51 patients continued directly into the long-term treatment period of Study 302.

Results of 165-302

A total of 164 previously-treated pegvaliase-pqpz adult PKU patients (152 from Study 301 and 12 from other pegvaliase-pqpz trials) were potentially eligible for the randomized withdrawal period of Study 30 and continued treatment for up to 13 weeks. Eighty-six (52%) met the eligibility target of ≥ 20% reduction in blood Phe concentration from their pre-treatment baseline concentration and continued into the efficacy assessment period. The results for the primary endpoint are presented in Table 1.

[h] Neurocognitive and neuropsychiatric symptoms scores included ADHD RS-IV Inattention Subscale score (investigator-Rated) for subjects with a baseline score > 9, ADHD RS-IV Inattention Subscale score (investigator-rated) for all subjects, PKU Profile of Mood States (POMS; self-rated) Confusion Subscale score, PKU POMS (self-rated) Total Mood Disturbance (TMD) score, POMS TMD (self-rated) score.

Table 1: Primary Endpoint: LS Mean Change in Blood Phenylalanine Concentration (µmol/L) from Randomized Withdrawal Baseline to Week 8 in Adult Patients with PKU – Efficacy Assessment

Randomized Study Arm	Pre-treatment Baseline Mean (SD)	Study 302 Randomized Withdrawal Baseline Mean (SD)	Study 302 Randomized Withdrawal Week 8 Mean (SD)[i]	LS Mean Change from Study 302 Randomized Withdrawal Baseline to Week 8 (95% CI)	Treatment Difference in LS Mean Change[j] (95% CI) P-Value
Pegvaliase-pqpz 20 mg/day	1450.2 (310.5) n = 29	596.8 (582.7) n = 29	553.0 (582.4) n = 26	-23.3 (-156.2, 109.7)	-973.0 (-1204.2, -741.9) <0.0001
Placebo 20 mg/day	1459.1 (354.7) n = 14	563.9 (504.6) n = 14	1509.0 (372.6) n = 13	949.8 (760.4, 1139.1)	
Pegvaliase-pqpz 40 mg/day	1185.8 (344.0) n = 29	410.9 (439.9) n = 29	566.3 (567.5) n = 23	76.3 (-60.2, 212.8)	-588.5 (-830.1, -346.9) <0.0001
Placebo 40 mg/day	1108.9 (266.8) n = 14	508.2 (363.7) n = 14	1164.4 (343.3) n = 10	664.8 (465.5, 864.1)	

The primary endpoint of change in blood Phe compared with placebo was met (p<0.0001). The majority of subjects in the pooled active group sustained blood Phe reduction while no patients in the placebo group achieved this reduction.

Secondary endpoints did not reach statistical significance. It is likely that 8 weeks was not enough time to see any significant change in neurocognitive and neuropsychiatric symptom scores. Blood Phe reduction is an established surrogate endpoint that is known to predict clinical benefit in adults with PKU. The Applicant states pegvaliase-pqpz clinical data provides strong support of the correction of the underlying PAH deficiency. There is regulatory precedent with sapropterin that supports blood Phe as an established biomarker in patients with PKU. Substantial evidence exists of Phe lowering as a clinically meaningful endpoint from the PKU treatment guidelines, the literature, and from patients.

5 Risk Assessment & Safe-Use Conditions

The safety population is comprised of 285 subjects who received pegvaliase-pqpz in an induction/titration/maintenance regimen in phase 2 and 3 trials. In clinical trials, the rates of adverse reactions decreased over time while the rate of hypophenylalanemia increased over time. Adverse reaction rates were highest during the induction/titration phase compared to the maintenance phase.

[i] Patients who did not complete Phe assessment within the window for Week 8 were excluded

[j] Treatment difference compared to pooled pegvaliase-pqpz

Hypersensitivity AEs (HAEs) were common (approximately 93%) and included arthralgia, rash, urticaria, and pruritus. HAEs mostly occur early during the induction and titration phase and less frequently during maintenance therapy. The median duration of HAEs was 2 days and 91% of HAEs required no dose modification. Study drug discontinuation was highest in the first year of treatment with few subjects discontinuing after completing the first year of treatment. Discontinuation from the second year was 9% and 2% in the third year. Dropout rate in the first year dropped from 33% to 19% in phase 3 studies after implementation of required premedications and other safety mitigations. Other common adverse reactions include injection site reactions (93%), headache (51%), nausea (32%), abdominal pain (30%), vomiting (28%), cough (26%), hypophenylalaninemia (17%), myalgia (15%), lymphadenopathy (14%), and erythema (13%).

There was one death in the clinical development program, occurring in Study 301. The subject was a firefighter who was fatally electrocuted while on his ladder truck carrying a water hose. The investigator reported this event as not related to pegvaliase-pqpz treatment and the review team agrees with the Applicant's assessment.

5.1 ANAPHYLAXIS

Anaphylaxis was the most clinically important identified risk in the pegvaliase-pqpz development program. In clinical trials of pegvaliase-pqpz with induction/titration/maintenance dosing, 26 out of 285 (9%) patients experienced a total of 37 anaphylaxis episodes. The exposure-adjusted rate of anaphylaxis was highest during the induction and titration phases (0.15 episodes/person-years; 5% of patients with at least one episode) and decreased in the maintenance phase (0.04 episodes/person-years; 6% of patients with at least one episode). Signs and symptoms of anaphylaxis reported in clinical trials included syncope, hypotension, hypoxia, dyspnea, wheezing, chest discomfort/chest tightness, tachycardia, angioedema, throat tightness, skin flushing, rash, urticaria, pruritus, and persistent gastrointestinal symptoms. In clinical trials, anaphylaxis generally occurred with 1 hour after injection (84%, 28/37 episodes), however delayed episodes also occurred up to 48 hours after administration. Most episodes of anaphylaxis occurred within the first year of dosing (78%, 29/37 episodes), but cases also occurred after one year of dosing and up to 834 days (2.3 years) into treatment. All occurrences of anaphylaxis were managed successfully with the safe use conditions implemented in the clinical studies and all events resolved without sequelae. Management of anaphylaxis in clinical trials included auto-injectable epinephrine (54%, 20/37 episodes), corticosteroids (54%, 20/37 episodes), antihistamines (51%, 19/37 episodes), and/or oxygen (5%, 2/37 episodes). Eighteen out of the 26 (69%) patients who experienced anaphylaxis were re-challenged and 5 (28%) had recurrence of anaphylaxis.

Anaphylaxis requires immediate treatment with auto-injectable epinephrine should be prescribed to patients receiving pegvaliase-pqpz. Prescribers should instruct patients to keep auto-injectable epinephrine readily available at all times during pegvaliase-pqpz treatment, how to properly self-inject epinephrine if needed, and to seek immediate medical care upon its use. Prescribers should also consider the risks associated with auto-injectable epinephrine use when prescribing pegvaliase-pqpz. The risks and benefits of pegvaliase-pqpz should be considered when readministering pegvaliase-pqpz following an episode of anaphylaxis. If the decision is made to re-administer pegvaliase-pqpz, it is recommended that the first dose be administered under the supervision of a healthcare provider

equipped to manage anaphylaxis and closely observe the patient for at least 60 minutes following the dose. Prescribers can consider premedications with a H_1-receptor antagonist, H_2-receptor antagonist and/or antipyretic prior to each dose of pegvaliase-pqpz based upon clinical judgement. Prescribers may consider having an adult observer for patients who may need assistance in recognizing and managing anaphylaxis during pegvaliase-pqpz treatment. If an adult observer is needed, the observer should be present during and for at least 60 minutes after pegvaliase-pqpz administration, should be able to administer auto-injectable epinephrine, and to call for emergency medical support.

5.2 Embryo-Fetal Toxicity and Adverse Developmental Outcomes

Based on findings from animal studies, pegvaliase-pqpz may cause fetal harm when administered during pregnancy. In animal reproduction studies, subcutaneous administration of pegvaliase-pqpz to pregnant rats during organogenesis resulted in adverse developmental outcomes at the 1.4 times the maximum recommended dose. In pregnant rabbits, subcutaneous administration of pegvaliase-pqpz during organogenesis resulted in a high incidence of malformations throughout the skeletal system, and in the kidneys, lungs, and eyes. Embryo-fetal toxicity (increased resorptions and reduced fetal weight) was also observed. These effects occurred at 7.5 times the maximum recommended daily dose, and were associated with strong signs of maternal toxicity, including marked reductions in weight gain and food consumption, and death. This raises concern about the potential adverse developmental outcomes in humans.

The estimated background risk of major birth defects and miscarriage for women with PKU with blood Phe ≥ 600 µmol/L is greater than the background risk for women without PKU. Uncontrolled blood Phe before and during pregnancy is associated with an increased risk of adverse pregnancy outcomes including miscarriage, major birth defects (microcephaly, major cardiac malformations), intrauterine fetal growth retardation and future intellectual disability with low IQ. Due to the limitation of understanding of the impact of pegvaliase-pqpz compared to the impact of blood Phe level on the potential for embryo-fetal toxicity, a REMS for this risk is not recommended at this time. The Applicant has proposed a pregnancy pharmacovigilance program to monitor outcomes in patients exposed to pegvaliase-pqpz during pregnancy.

6 Expected Postmarket Use

Pegvaliase-pqpz is likely to be prescribed by specialists familiar with the treatment of PKU. The labeling will state that pegvaliase-pqpz should be initially administered under the supervision of a healthcare provider equipped to manage anaphylaxis and the patient should be closely observed for 60 minutes following injection. This instruction is so that prior to self-injection, healthcare providers may confirm patient competency with self-administration, the patient's ability to recognize signs and symptoms of anaphylaxis and ability to administer auto-injectable epinephrine. After confirmation of self-injection technique and counseling and training on how to recognize and respond to signs and symptoms of anaphylaxis, pegvaliase-pqpz will be administered by the patient or the patient's caregiver at the patient's home. The patient is required to have auto-injectable epinephrine readily available at all times during pegvaliase-pqpz treatment.

The Applicant further proposes that a responsible adult (b) (4) be available to observe the patient at the time and for 60 minutes following pegvaliase-pqpz administration (b) (4) (b) (4) during self-administration and that the patient (b) (4) take premedications including an H1 blocker, H2 blocker, and antipyretic (b) (4) (b) (4). The review team agrees that these additional measures may be useful for some patients and can be implemented at the prescriber's discretion using clinical judgement, but should not be required for all patients. See section 8 for further details.

7 Risk Management Activities Proposed by the Applicant

The Applicant proposed risk management activities for pegvaliase-pqpz beyond routine pharmacovigilance and labeling including a REMS with ETASU to mitigate the risk of anaphylaxis.

7.1 Review of Applicant's Proposed REMS

BioMarin submitted a complete REMS proposal including a REMS document, supporting document and appended materials with their original BLA submission dated June 30, 2016 and amended March 9, 2018, March 15, 2018, April 5, 2018, April 23, 2018, April 24, 2018, May 7, 2018, May 15, 2018, May 18, 2018, and May 22, 2018. The REMS contains prescriber certification, pharmacy certification, the requirement that pegvaliase-pqpz should not be dispensed to patients without documentation or evidence of safe use conditions defined as patient enrollment and counseling and auto-injectable epinephrine, an implementation system, and a timetable for submission of assessments.

The Applicant's proposed REMS structure is based on an amendment enacted during their clinical development program wherein they initiated additional strategies to mitigate the risk of anaphylaxis. These strategies included mandatory premedication, mandatory access to auto-injectable epinephrine, a responsible adult to observe the patient for one hour post injection (b) (4) and education to recognize the signs and symptoms of anaphylaxis.

7.1.1 REMS Goals

The applicant proposed the following goal for the Palynziq REMS Program:

The goal of the Palynziq REMS is to mitigate the serious outcomes of anaphylaxis by:

- Ensuring that prescribers are educated about the risk of anaphylaxis, and the importance of premedication
- Ensuring that prescribers are educated about the need to counsel patients about the risk, the need for a trained observer and the need for auto-injectable epinephrine
- Ensuring that Palynziq is only dispensed to patients with documentation of safe use conditions

Reviewer's Comments: *the REMS goal has been revised to the following:*

The goal of the Palynziq REMS is to mitigate the risk of anaphylaxis associated with Palynziq by:

- *Ensuring prescribers are educated on the risk of anaphylaxis associated with the use of Palynziq.*
- *Ensuring that prescribers are educated and adhere to the following:*

- *Counsel patients on how to recognize and respond to signs and symptoms of anaphylaxis*
- *Enroll patients in the Palynziq REMS Program*
- *Prescribe auto-injectable epinephrine with Palynziq*

- *Ensuring that Palynziq is only dispensed to patients with documentation of safe use conditions including:*
  - *Patient education and enrollment*
  - *Having auto-injectable epinephrine with available at all times*
- *Ensuring that patients are educated on the following:*
  - *How to recognize and respond to signs and symptoms of anaphylaxis*
  - *The need to carry auto-injectable epinephrine with them at all times*

7.1.2 Medication Guide

(b) (4) (b) (4) Office of Medical Policy Patient Labeling team will review the MG under their review of the label for BLA 761079. The MG will be dispensed with each Palynziq prescription in accordance with 21CFR 208.24. The MG will be packaged with each unit of use and will be available to all stakeholders via the Palynziq REMS website.

Reviewer Comments*: The MG is not required as an element of the REMS, as there will be patient materials developed that are focused specifically on the REMS risk. The MG should, however, be* (b) (4) (b) (4) *part of the product labeling*.

7.1.3 Elements to Assure Safe Use (ETASU)

The Applicant has proposed ETASU to include prescriber enrollment (A), pharmacy enrollment (B), and documentation of safe-use conditions (D). The proposed safe use conditions include patient enrollment and counseling and auto-injectable epinephrine.

Reviewer Comments*: The Agency agrees that the REMS should include the above ETASU. Prescriber certification will ensure that prescribers are informed about the risk and the need to counsel and enroll patients, as well as prescribe each patient auto-injectable epinephrine. Pharmacy certification will ensure that patients and prescribers are enrolled prior to dispensing. Additionally, the pharmacy will verify that patients have access to auto-injectable epinephrine. The safe use conditions will ensure that patients are counseled about the risk and will have auto-injectable epinephrine available during treatment with pegvaliase-pqpz. We do not agree with the other proposed safe use conditions,* (b) (4) (b) (4)*, as they will not ensure that the benefits of pegvaliase-pqpz outweigh the risks (See further comment in Section 8). The impact of these interventions on the anaphylaxis rate was uncertain in the clinical trials and the inclusion* (b) (4) *pose additional undue burden. We acknowledge that these interventions may be beneficial for certain patients and agree that information about their use can be included in the REMS materials as options for prescribers to consider, as outlined in the product labeling.*

7.1.4 Implementation System

The Applicant has proposed to include an implementation system including maintenance of a validated, secure database of enrolled patients and certified prescribers and pharmacies, a Palynziq REMS coordinating center, and a Palynziq REMS website.

Reviewer Comments*: The agency agrees than an implementation system is necessary for the REMS program as it contains ETASU B and D.*

7.1.5 Timetable for Submission of Assessments

BioMarin proposes to submit assessments to the FDA at 6 months and 12 months post approval of the REMS and annually thereafter from the date of the initial approval of the Palynziq REMS.

Reviewer Comments*: The proposed timetable for submission of assessments is acceptable*.

7.1.6 REMS Materials & Key Risk Messages

We have reviewed the following REMS Program materials submitted by BioMarin:

- Prescriber Enrollment Form
- Patient Enrollment Form
- Pharmacy Enrollment Form
- Prescriber Guide
- Prescriber Knowledge Assessment
- Patient Guide
- Safety Video Transcript
- Safety Video Storyboard
- Wallet Card
- REMS Program Overview
- Website Screenshots

Reviewer's Comments: *When initially submitted, the Applicant did not include the following REMS materials: Pharmacy Enrollment Form to ensure that pharmacies who wish to enroll in the REMS program document their agreement to the requirements via attestations, a Program Overview to explain the role of each stakeholder in the REMS, a patient directed Safety Video to further convey the risk of anaphylaxis to patients, and a Prescriber Knowledge Assessment to ensure that prescribers understand the risk of anaphylaxis and their role in the PALYNZIQ REMS. The Agency informed the Applicant of these requirements, and they were included in the May 22, 2018 submission. All other initially submitted materials were agreed to be necessary by the Agency. Further, the Applicant has included key risk messages that need to be conveyed.*

7.1.7 REMS Assessment Plan

Reviewer's Comments: *The REMS Assessment Plan as submitted on May 22, 2018 is acceptable*.

ASSESSMENT PLAN

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 fax
    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 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 prescriber's 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 actions (CAPA) plans, and the status of CAPA plans
2. Number of prescribers and pharmacies and distributors de-certified and 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 report, 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, to include 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, source of report, resulting corrective and preventive actions (CAPA)

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.

7.2 Other Proposed Risk Management Activities

The applicant proposed the following risk management activities:

- Routine Pharmacovigilance
    - Continuous monitoring of the benefit-risk profile of pegvaliase-pqpz including assessment of aggregate safety data and taking appropriate actions in response, and communicating emerging safety concerns to applicable health authorities
    - Individual case safety report management which involves collection, collation, follow-up, assessment and regulatory reporting of suspected adverse drug reactions from any source
    - Signal management to identify, evaluate, validate and act upon previously unrecognized risks
    - Study management, which includes active monitoring of adverse events and relevant laboratory test values in ongoing clinical studies, and planned post-marketing studies
- Additional Pharmacovigilance Activities
    - Completion of ongoing studies

Reviewer's Comments: *We note that these other activities proposed by the applicant are outside of the scope of the REMS program and defer to the Division of Pharmacovigilance for review and input.*

8 Discussion of Need for a REMS

PKU is a serious genetic disorder which, if untreated, can cause intellectual disability, developmental, behavioral, and psychiatric dysfunction. Current treatment options include a Phe-restricted diet and sapropterin, a synthetic BH4 cofactor, the only FDA-approved drug for PKU. Although a Phe-restricted diet is generally efficacious and well tolerated in children with PKU, most adults with PKU have poor adherence to this strict diet and many patients do not respond to treatment with sapropterin. As such, there is an unmet medical need in the general adult population with PKU.

The clinical data presented in the BLA generally demonstrate a statistically and clinically significant reduction in Phe levels in most enrolled patients in the pivotal Study 302, part 2. In those patients who reach a target maintenance dose and meet eligibility criteria, the 20 mg and 40 mg treatment arms maintained Phe reduction while the placebo arms had Phe elevation to pretreatment levels. If patients respond to pegvaliase-pqpz treatment, they may be able to liberalize their restricted diet. This would have psychosocial implications such as not having to calculate protein/Phe intake, eating meals with others, and a more palatable diet. In addition, a more normal diet will promote better overall health in patients with PKU and will help to avoid nutritional and vitamin deficiencies caused by the Phe-restricted diet over the long term. Pegvaliase-pqpz will provide effective therapy for the treatment of

PKU, which is a serious unmet need in adult PKU patients who are unable to control their blood Phe levels on available existing therapy.

Pegvaliase-pqpz is associated with high rates of hypersensitivity AEs (93%) and anaphylaxis (9%). The proposed labeling for pegvaliase-pqpz has been maximized and includes a Boxed Warning, MG, a narrow indication to those who have uncontrolled blood Phe levels on existing management, a maximum recommended dose, and discontinuation for lack of efficacy. However, further risk mitigation in the form of a REMS is necessary to ensure that prescribers and patients are aware of the risk and that safe use requirements are met before administration of pegvaliase-pqpz. The safety concern of anaphylaxis and the Applicant's proposed REMS were discussed on December 13, 2017 at the meeting of the REMS Oversight Committee (ROC)[k]. The ROC concurred that additional risk mitigation measures beyond labeling including a REMS with ETASU are necessary to ensure the benefits of pegvaliase-pqpz outweigh the serious risk of anaphylaxis.

DRISK and DGIEP agree that labeling alone will not ensure that prescribers and patients are informed of the risk of anaphylaxis and that patients have access to auto-injectable epinephrine prior to starting pegvaliase-pqpz. A REMS will ensure that both the prescriber and patient are informed about the risk of anaphylaxis. The REMS will be used to educate patients on how to recognize and respond to signs and symptoms of anaphylaxis and ensure that they have auto-injectable epinephrine as a safe use condition. Auto-injectable epinephrine must be prescribed to all patients receiving pegvaliase-pqpz and should be readily available at all times during pegvaliase-pqpz treatment. The proposed labeling recommends co-prescribing of auto-injectable epinephrine in the Warning and Precautions section and Boxed Warning, however, the additional requirement provided by a REMS will help to ensure that all patients have access to auto-injectable epinephrine while on pegvaliase-pqpz therapy.

The minimum necessary elements required include:

1. Prescriber certification (ETASU A) to ensure that each prescriber is informed of the risk of anaphylaxis, the need to counsel patients about the risk, and the need to prescribe auto-injectable epinephrine.
2. Pharmacy certification (ETASU B) to ensure that patients and prescribers are enrolled or certified in the program and thus aware of the risk of anaphylaxis, and to verify that the patient has auto-injectable epinephrine prior to dispensing the product.
3. Safe-use conditions (ETASU D) include patient enrollment to ensure that each patient is counseled and trained on how to recognize and respond to anaphylaxis and that each patient has auto-injectable epinephrine available at all times.

Appended materials will include: a prescriber enrollment form, prescriber guide, prescriber knowledge assessment, a program overview, pharmacy enrollment form, patient enrollment form, patient guide, safety video, wallet card, and a website. Enrollment forms will include attestations for each relevant

[k] As per the 21st Century review process, all REMS with elements to assure safe use (ETASU) are discussed at the REMS Oversight Committee (ROC), which consists of senior-level management from the Offices of New Drugs, Surveillance and Epidemiology, and Regulatory Policy.

stakeholder regarding knowledge of the REMS risks, as well as the safe use conditions required before dispensing and administration of the product. The prescriber knowledge assessment will ensure that prescribers understand the key messages included in the prescriber training at the time they take the assessment.

The Program Overview will be a concise document for any stakeholder to reference for REMS program operations and requirements. Patient directed materials include a wallet card, a safety video, and a patient guide to present information about the risk and what to do in the event they experience anaphylaxis, and that they must have auto-injectable epinephrine available at all times during treatment. Finally, a REMS website will assist in operationalizing the program by having all materials available and having online enrollment available. Further, an implementation system and timetable for submission of assessments will be requirements included in this REMS.

Due to uncertainty of its effect on the anaphylaxis rate in clinical trials and the questionable real-world feasibility, the (b) (4) (b) (4) Agency concluded that the use of monitoring by a trained observer (b) (4) (b) (4) will not mitigate the risk of anaphylaxis for patients using pegvaliase-pqpz. (b) (4) (b) (4) (b) (4) Other allergic conditions such as severe food allergies, bee sting allergies, or other drug allergies do not require an observer and are also unpredictable much like the anaphylactic events seen in the pegvaliase-pqpz clinical trials. Although the use of an observer was recommended by the review team to incorporate into the clinical trials in response to anaphylactic events, after further review of the data, at this time, the Agency does not recommend that use of an observer should be required for all patients taking pegvaliase-pqpz and does not recommend it be included as a safe use condition in the REMS. The Agency's current thinking is that the need for an observer should be determined by the healthcare provider based on individual patients' needs.

Similarly, due to uncertainty of their effect on the anaphylaxis rate in clinical trials and the questionable real-world feasibility, (b) (4) premedications will not be included as a requirement in the REMS. Although the use of premedications may provide symptomatic relief of hypersensitivity-associated clinical findings such as rash, itching, and fever, the benefits do not outweigh the risks of required premedications for all patients using pegvaliase-pqpz and anaphylaxis events continued to occur despite patients using premedications. The Agency is concerned that the long term use of the recommended pre-medications, specifically non-steroidal anti-inflammatories (NSAIDS), is associated with serious safety risks including gastrointestinal ulcer, cardiovascular risk, and bleeding. Additionally, the use of multiple medications may mask the early signs of hypersensitivity or anaphylaxis as well as may result in pill burden for patients. After further review of the data, at this time, the Agency does not recommend that premedications should be required for all patients taking pegvaliase-pqpz and does not recommend that they be included as a safe use conditions in the REMS. The Agency concludes that it should be per the prescriber's digression whether their patient could benefit from the use of premedications and specifically which premedications to use.

Therefore, a REMS with ETASU A, B, D, an implementation system and a timetable for submission of assessments is necessary for the benefits of pegvaliase-pqpz to outweigh the risk of anaphylaxis.

9 Conclusion & Recommendations

The risk of anaphylaxis associated with pegvaliase-pqpz is serious. Prescribers must understand this risk, the importance of patient counseling and ensure that the patient has access to auto-injectable epinephrine. Based on the magnitude and severity of the risk of anaphylaxis, a REMS with ETASU is necessary to ensure that the benefits outweigh the risks.

Prescriber certification (ETASU A) will ensure that prescribers are informed of the risk of anaphylaxis and the need to provide counseling to patients about the risk prior to initiation of pegvaliase-pqpz and have ordered appropriate auto-injectable epinephrine for each patient. Pharmacy certification (ETASU B) will ensure that prescribers are certified and therefore aware of the risk of anaphylaxis. Additionally, pharmacy certification will help to ensure that the safe use conditions are met by verifying that patients have been enrolled into the program by their prescriber and confirming that the patient has auto-injectable epinephrine before dispensing pegvaliase-pqpz. Safe use conditions (ETASU D) will include patient enrollment to ensure patients are aware of the risks and have been counseled, and that they have auto-injectable epinephrine available at all times during treatment. Additionally, the REMS will require an implementation system and timetable for submission of assessments.

DRISK finds the Applicant's proposed REMS as submitted on May 22, 2018 to be acceptable and is appended to this review.

10 APPENDICES

10.1 REFERENCES

[1] Buracchio T, Dimick-Santos, L. Safety Memo, Division of Gastroenterology and Inborn Errors Products for IND 076269, dated May 14, 2014.

[2] Mulberg, A. Advice Information Request, IND 076269, dated May 14, 2014

[3] BioMarin. Orig-1 for BLA 761079. June 30, 2017

[4] Vali, B. BLA 761079 – Palynziq (pegvaliase-pqpz) for PKU: Request for Information. July 31, 2017

[5] Roman, D. Priority Review Designation for BLA 761079. August 29, 2017

[6] Griebel, D. Filing Review Issues Identified for BLA 761079. September 12, 2017

[7] Vockley J, Andersson HC, Antshel KM, Braverman NE, Burton BK, et al. ACMG Practice Guidelines: Phenylalanine hydroxylase deficiency: diagnosis and management guideline. Genet Med. 2014 Jan;16(2):188-200

[8] Moyle JJ, Fox AM, Arthur M, Bynevel M, Burnett JR. Meta-Analysis of Neuropsychological Symptoms of Adolescents and Adults with PKU. Neuropsychol Rev. 2007 Jun;17(2):91-101

[9] ten Hoedt AE, de Sonneville LM, Francois B, ter Horst NM, Janssen MC, et al. High phenylalanine levels directly affect mood and sustained attention in adults with phenylketonuria: a randomized, double-blind, placebo-controlled, crossover trial. J Inherit Metab Dis. 2011 Feb;34(1):165-71

[10] American Academy of Pediatrics. Committee on Genetics. Maternal phenylketonuria. Pediatrics. 2001 Feb;107(2):427-8

[11] Vockley J, Andersson HC, Antshel KM, Braverman NE, Burton BK, et al. ACMG Practice Guidelines: Phenylalanine hydroxylase deficiency: diagnosis and management guideline. Genet Med. 2014 Jan;16(2):188-200

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