

New Drug Evaluation: Pegvaliase-pqpz injection, subcutaneous

Date of Review: September 2018

Generic Name: pegvaliase-pqpz

End Date of Literature Search: 06/27/2018

Brand Name (Manufacturer): Palynziq™ (BioMarin Pharmaceutical Inc.)

Dossier Received: yes

Research Questions:

1. What is the efficacy of pegvaliase compared to placebo or currently available treatments for phenylketonuria (PKU)?
2. Is pegvaliase safe for the treatment of PKU?
3. Are there any subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) that would particularly benefit or be harmed from treatment with pegvaliase?

Conclusions:

- Efficacy evidence for pegvaliase comes from one discontinuation trial (n=86) with high risk of selection bias in which patients were randomized to either discontinue or maintain treatment with pegvaliase.¹
- Low quality of evidence found a statistically significant difference in the increase of blood phenylalanine levels in PKU patients stable on pegvaliase from the beginning of the discontinuation trial to week 8 in the pooled pegvaliase group (26.5 µmol/L) compared to the 20 mg/day and 40 mg/day placebo groups (949.8 µmol/L and 664.8 µmol/L, respectively; p=0.0001 for both groups vs. pooled pegvaliase).¹ The pooled pegvaliase group remained at near the same levels as the beginning of the randomized discontinuation trial (<600 µmol/L) while placebo groups experienced an increase in levels to values higher than the American College of Medical Genetics and Genomics (ACMG) guideline-recommended lifetime phenylalanine goal of 120-360 µmol/L and also higher than the United States Food and Drug Administration (FDA)-approved PKU indication for initiation of pegvaliase (>600 µmol/L on existing management).¹⁻³
- There is insufficient evidence to determine differences in neuropsychiatric or neurocognitive symptoms as measured by the Attention Deficit Hyperactivity Disorder Rating Scale IV inattention subscale (ADHD RS-IV IA) and Profile of Mood States (POMS) scores including POMS, PKU-POMS, and PKU-POMS confusion subscale score in patients treated with pegvaliase versus placebo.¹ Results were not statistically significant for these outcomes.¹
- Safety concerns with pegvaliase include anaphylaxis, which occurred in 9% (n=26) of patients treated with pegvaliase in the FDA safety analysis (n=285).³ Pegvaliase has a boxed warning regarding anaphylaxis, is only available through a Risk Evaluation and Mitigation Strategy (REMS) program, and requires that patients prescribed pegvaliase are also prescribed auto-injectable epinephrine.³
- There is insufficient direct evidence to determine comparative efficacy of pegvaliase and sapropterin for PKU.
- There is insufficient evidence to determine if any subgroups would particularly benefit or be harmed from treatment with pegvaliase.

Recommendations:

- Implement prior authorization criteria for pegvaliase (**Appendix 2**).

Background:

Phenylketonuria (PKU) is an autosomal recessive disorder caused by an error in amino acid metabolism.⁴ Patients with PKU have a deficiency of phenylalanine hydroxylase, which results in increased levels of phenylalanine in the blood and brain.⁵ PKU has an incidence of 1 in 15,000 live births in the United States and in the Oregon Health Plan (OHP) fee-for-service (FFS) population there are over 200 patients with diagnoses of PKU.⁵ While newborn PKU screening is recommended by the U.S. Preventive Services Task Force and rarely untreated, if undiagnosed or untreated PKU symptoms include severe mental retardation, developmental delays, epilepsy, behavioral problems, eczema-like dermatologic problems, and a mousy odor (due to the buildup of phenylalanine).^{5,6} Once hyperphenylalaninemia is identified in a newborn screening, plasma amino acid analysis is completed to confirm elevated phenylalanine concentrations and then additional tests are completed to differentiate PKU from other causes of hyperphenylalaninemia.² Genotyping is then completed to determine metabolic phenotype and extent of recommended dietary phenylalanine restriction as well as the likelihood of response to tetrahydrobiopterin (BH4; sapropterin) supplementation.²

The 2014 American College of Medical Genetics and Genomics (ACMG) PKU guidelines recommend treatment initiation for patients with phenylalanine levels greater than 360 $\mu\text{mol/L}$.² However, some treatment centers may not initiate treatment unless levels are greater than 600 $\mu\text{mol/L}$ given mixed evidence of outcomes for untreated patients with levels between 360 and 600 $\mu\text{mol/L}$.² Treatment initiation is recommended upon diagnosis, preferably within the first week of life, with the goal of achieving control in the first 2 weeks of life.² Initial treatment usually includes excluding phenylalanine from the diet until within the goal range, and implementation of a phenylalanine-restricted diet afterwards.² Relaxation of phenylalanine control later in life and subsequent buildup of phenylalanine can result in neurocognitive and psychiatric symptoms, and therefore the goal of treatment is to maintain lifelong blood phenylalanine levels of 120-360 $\mu\text{mol/L}$.² While lower than the normal range, levels of 60-120 $\mu\text{mol/L}$ are not considered too low based on available evidence, but phenylalanine levels less than 30 $\mu\text{mol/L}$ should be avoided.² Symptom improvement usually occurs with a reduction of phenylalanine levels.² Recommended blood phenylalanine monitoring frequencies based on age are listed in **Table 1**.²

Table 1. Recommended Frequency of Blood Phenylalanine Levels Based on Patient Age²

Age	Frequency of Monitoring
Newly diagnosed infants	Frequently until levels are stabilized
Less than 1 year	At least weekly
1-12 years	Biweekly to monthly
Adolescents and adults with stable levels	Monthly

Dietary restriction of phenylalanine is the mainstay of therapy.² Foods which contain phenylalanine and should be restricted include meat, fish, milk, cheese, eggs, nuts, flour, soy, and drinks with aspartame.^{4,5} Medical food products containing phenylalanine-free amino acid mixtures are also recommended to meet established dietary requirements.^{2,5}

Sapropterin dihydrochloride (Kuvan[®]) was approved in 2007 by the U.S. Food and Drug Administration (FDA) to lower blood phenylalanine levels in patients with hyperphenylalaninemia due to BH4-responsive PKU in conjunction with a phenylalanine-restricted diet.⁷ Sapropterin works by activating residual phenylalanine hydroxylase activity to improve the metabolism of phenylalanine, and therefore decrease phenylalanine levels.⁷ It was the first medication indicated for PKU at

the time of its approval. Around 25-50% of patients with PKU are responsive to sapropterin, and genotyping may be predictive of response.^{2,7} In sapropterin clinical trials, response was defined as at least a 30% decrease in blood phenylalanine levels from baseline.⁷

Large neutral amino acids (LNAA) may also be used for PKU therapy, but larger trials are necessary to determine safety and efficacy.² LNAAs are available in several formulations and are classified as a medical food, which are not reviewed by the FDA.⁸

Pegvaliase-pqpz (Palynziq™) is a recently FDA-approved medication indicated to reduce blood phenylalanine concentrations in adult patients with phenylketonuria who have uncontrolled blood phenylalanine concentrations greater than 600 µmol/L on existing management.³

See **Appendix 1 for Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies, indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Pegvaliase is a phenylalanine-metabolizing enzyme approved by the FDA in May 2018 indicated to reduce blood phenylalanine concentrations in adult patients with PKU who have uncontrolled phenylalanine concentrations greater than 600 µmol/L on existing management.³ Approval was based on two phase 3 trials, PRISM-1 and PRISM-2.^{1,9,10}

PRISM-1 was an open-label, parallel group phase 3 study in which patients were administered with an induction, titration, and maintenance dosing regimen of either pegvaliase 20 mg/day or 40 mg/day.⁹ The primary outcome of PRISM-1 was focused on safety which will not be discussed in this section but is included in the FDA safety analysis.^{3,9} If a patient was unable to titrate to or maintain their randomized pegvaliase 20 mg/day or 40 mg/day dose in PRISM-1 (n=16), they were enrolled into PRISM-2 Part 4 for the open-label extension period and were not included in PRISM-2 Parts 1-3 described below.^{1,9} Another 54 patients also discontinued pegvaliase early in PRISM-1 due to adverse events (n=29), withdrawal by patient, physician decision, pregnancy, protocol deviation, loss to follow-up, or another reason and did not enter PRISM-2 at all.⁹

PRISM-2 was a four-part phase 3 clinical study of pegvaliase.^{1,9} Part 1 was an open-label continuation of PRISM-1 where patients remained on their maintenance 20 mg/day or 40 mg/day regimen of pegvaliase and eligibility to enter Part 2 was assessed.⁹ Part 2 of PRISM-2 was a double-blind, placebo-controlled, randomized discontinuation trial in which patients remained on their 20 mg/day or 40 mg/day regimen of pegvaliase from Part 1 or were randomized to a matching placebo.⁹ In Part 3, any patients randomized to placebo returned to their 20 mg/day or 40 mg/day regimen of pegvaliase from Part 1 for pharmacodynamic and pharmacokinetic analyses.⁹ Finally, Part 4 was an open-label extension period to assess long term outcomes.⁹ The focus of the FDA efficacy review was on PRISM-2 Part 2, which is described and evaluated below in **Table 4**, as it was the only placebo-controlled period of the phase 3 trials.^{1,10}

The randomized discontinuation trial in PRISM-2 Part 2 enrolled patients who were stable on pegvaliase 20 mg/day or 40 mg/day from PRISM-1 who also achieved a blood phenylalanine reduction of at least 20% (from mean of 2 consecutive blood phenylalanine assessments) from treatment-naïve baseline at the time of discontinuation trial entry.¹ Included patients (n=86) were 18 years of age and older with PKU.¹ Prior to PRISM-1, patients were required to discontinue any sapropterin or large neutral amino acids and any neuropsychiatric medications were required to be at stable doses.¹ Patients were provided with epinephrine injectors for use in case of acute systemic hypersensitivity events.¹ A statistically significant difference was found in the primary endpoint of change in blood phenylalanine levels at week 8 with the pooled pegvaliase group (26.5 µmol/L) compared to the 20 mg/day and 40 mg/day placebo groups (949.8

μmol/L and 664.8 μmol/L, respectively; p=0.0001 for both groups vs. pooled pegvaliase).¹ The pooled pegvaliase group remained at near the same levels as the beginning of the randomized discontinuation trial (<600 μmol/L) while placebo groups experienced an increase in levels to values higher than the ACMG guideline-recommended lifetime phenylalanine goal level of 120-360 μmol/L and also higher than the United States Food and Drug Administration (FDA)-approved PKU indication for initiation of pegvaliase (>600 μmol/L on existing management).¹⁻³

Secondary endpoints for the trial included neuropsychiatric or neurocognitive symptoms as measured by the Attention Deficit Hyperactivity Disorder Rating Scale IV inattention subscale (ADHD RS-IV IA) and Profile of Mood States (POMS) scores.¹ The ADHD-RS-IV IA was administered by investigators (scale 0-27; higher scores indicate greater impairment) while the POMS instrument was self-administered by study participants (scale -32 to 200; higher scores indicate greater mood symptoms).¹ No statistically significant differences were found in these secondary endpoints or additional PKU-specific POMS scales, PKU-POMS and PKU-POMS confusion subscale score.¹ The FDA clinical review noted that the lack of significant results may be due to the small sample size and short 8 week duration.¹⁰ There may also be limitations in patient-reporting of symptoms in the scales used due to self-awareness concerns based on phenylalanine control.¹

PRISM-1 and PRISM-2 Combined Analysis

A combined analysis of PRISM-1 and PRISM-2 reported that that within 24 months, 64.8% of patients treated with pegvaliase achieved blood phenylalanine levels of 600 μmol/L or lower, 60.7% achieved levels of 360 μmol/L or lower, and 51.2% achieved levels of 120 μmol/L or lower.⁹ Statistical significance of these results was not reported.⁹ Levels of 120-360 μmol/L are clinically significant as this is the ACMG guideline-recommended lifetime goal for phenylalanine levels.²

An analysis was also completed by the FDA to determine how long it took patients with a pre-treatment blood phenylalanine level of over 600 μmol/L to achieve a first response, as defined by at least a 20% reduction in blood phenylalanine concentration from pre-treatment baseline or a blood phenylalanine level of 600 μmol/L or lower.¹⁰ Of 118 patients who received a dose of pegvaliase 20 mg/day, 70% (n=81) reached their first response between 4 and 24 weeks of 20 mg/day treatment.¹⁰ Of the 118 patients, 25 later escalated their dose to 40 mg/day and of those, 56% achieved their first response after 4-16 weeks of 40 mg/day treatment.¹⁰

Limitations

Both PRISM-1 and PRISM-2 were funded by BioMarin Pharmaceutical Inc., the manufacturer of pegvaliase.^{1,9} Limitations of PRISM-2 Part 2 include a high overall attrition rate (16.3%) in a trial of short duration (8 weeks).¹ Additionally, this trial does not provide data on the maximum blood phenylalanine level lowering ability of pegvaliase as patients treated in Part 2 had already been stable on 20 mg/day or 40 mg/day of pegvaliase.¹ Furthermore, there is a risk of selection bias due to the structure of the trials in that patients who could not titrate to or maintain a maintenance dose of pegvaliase were not included in the PRISM-2 Part 2 discontinuation trial.⁹ Patients who did not achieve a blood phenylalanine reduction of at least 20% (from mean of 2 consecutive blood phenylalanine assessments) from treatment-naïve baseline at the time of randomized discontinuation trial entry were also not included in PRISM-2 Part 2, adding to the risk of selection bias.⁹ Efficacy of pegvaliase in combination with or compared to sapropterin remains unknown as patients were required to discontinue sapropterin use prior to pegvaliase trials.^{1,9} Efficacy and safety of pegvaliase in pediatric patients is also unknown as only patients 18 years and older were included in the PRISM-1 and PRISM-2 trials, which is significant as PKU is diagnosed and treated early in life.^{1,3,9} Long-term efficacy of pegvaliase remains unclear as the randomized discontinuation trial was limited to 8 weeks.¹ However, long-term extension trials are ongoing.⁹

Dietary Restriction of Phenylalanine

FDA labeling recommends monitoring of dietary protein and phenylalanine intake but does not specifically require monitoring or dietary restrictions during pegvaliase treatment.³ Patients should be counseled on how to adjust their dietary intake of phenylalanine if needed based on their blood phenylalanine levels.³

Clinical Safety:

The most common adverse reactions ($\geq 20\%$) with pegvaliase treatment were injection site reactions, arthralgia, hypersensitivity reactions, headache, generalized skin reactions lasting at least 14 days, pruritus, nausea, abdominal pain, oropharyngeal pain, vomiting, cough, diarrhea, and fatigue.³ The incidence of most common adverse reactions is summarized in **Table 2**.³ During the induction/titration/maintenance regimen of trials, 11% of patients (n=31) discontinued treatment due to adverse reactions, with the most common reason being hypersensitivity reactions (6% of patients; 3% anaphylaxis).³ Arthralgia and hypersensitivity reactions were the most common events leading to dose reduction (14% and 9% of patients, respectively).³

Table 2. Adverse Reactions Reported in at Least 20% of PKU Patients Treated with Pegvaliase in Either the Induction/Titration Phase or Maintenance Phase³

Adverse Reaction	Induction/Titration Phase (N=285), %	Maintenance Phase (N=223); %
Injection site reactions	88%	72%
Arthralgia	74%	61%
Hypersensitivity reactions	53%	61%
Headache	35%	50%
Generalized skin reaction lasting ≥ 14 days	21%	37%
Pruritis	20%	24%
Nausea	18%	26%
Abdominal pain	14%	25%
Oropharyngeal pain	13%	23%
Fatigue	13%	22%
Vomiting	13%	26%
Cough	9%	22%
Diarrhea	9%	22%

FDA-approved labeling for pegvaliase includes a boxed warning for risk of anaphylaxis as it has been reported after administration and may occur at any time.³ In clinical trials, 9% of patients (n=26) experienced anaphylaxis, with a total of 37 anaphylaxis episodes.³ Anaphylaxis most commonly occurred within 1 hour of injection (84%; 28/37 episodes) but delayed episodes also occurred up to 48 hours after administration of pegvaliase.³ A majority of episodes occurred during the first year of pegvaliase use (78%; 29/37 episodes), but cases also occurred up to 2.3 years into treatment.³ Management of anaphylaxis included auto-injectable epinephrine (54%), corticosteroids (54%), antihistamines (51%), and oxygen (5%).³ Of those who experienced anaphylaxis, 18 (69%) were re-challenged with pegvaliase treatment and 28% of those patients (n=5) had recurrence of anaphylaxis.³ It is recommended to administer the initial dose of pegvaliase under the supervision of a healthcare provider equipped to manage anaphylaxis with observation of the patient for at least an hour after injection.³ Additionally, auto-injectable epinephrine should be prescribed concurrently with pegvaliase. Due to these anaphylaxis concerns, pegvaliase is only available through a REMS program.³

Other hypersensitivity reactions also occurred in 69% of pegvaliase-treated patients. Rates were highest in the induction and titration phases (4.5 episodes/person-year; 50% of patients with at least 1 adverse reaction) and decreased in the maintenance phase (1.5 episodes/person-year; 57% of patients

with at least 1 adverse reaction).³ The FDA clinical review noted hypersensitivity adverse events were likely drug-related due to the product's immunogenicity.¹⁰ H₁-receptor antagonist, H₂-receptor antagonist, and/or antipyretics may be considered for premedication based on patient tolerability.³

FDA safety data includes 229 patients exposed to pegvaliase for 24 weeks, 209 patients exposed for 1 year, 137 patients exposed for 2 years, and 85 patients exposed for 3 years or longer.³ As pegvaliase has the potential to be a life-long medication, extended long-term safety is still unknown.³

Look-alike / Sound-alike Error Risk Potential: None identified.

Comparative Endpoints:

Clinically Meaningful Endpoints:

- 1) Neuropsychiatric symptoms
- 2) Serious adverse events
- 3) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Reduction in blood phenylalanine concentration

Table 3. Pharmacology and Pharmacokinetic Properties.³

Parameter	
Mechanism of Action	Pegylated phenylalanine ammonia lyase enzyme that converts phenylalanine to ammonia and <i>trans</i> -cinnamic acid. Works by substituting for the deficient phenylalanine hydroxylase enzyme activity in patients with PKU and reduces blood phenylalanine concentrations.
Oral Bioavailability	N/A- administered subcutaneously
Distribution and Protein Binding	Mean apparent volume of distribution: 26.4 L in 20 mg once daily dose; 22.2 L in 40 mg once daily dose
Elimination	Mean apparent clearance at steady state: 0.39 L/hour in 20 mg once daily dose; 1.25 L/hour in 40 mg once daily dose Route of elimination has not been studied in humans
Half-Life	Mean half-life: 47 hours in 20 mg once daily dose; 60 hours in 40 mg once daily dose
Metabolism	Catabolic pathways; expected to be degraded into small peptides and amino acids

Abbreviations: L = liter; N/A = not applicable

Table 4. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Harding CO, et al ¹ PRISM-2 Part 2: Randomized Discontinuation Trial	1. Pegvaliase 20 mg/d subq 2. Pegvaliase 40 mg/d subq 3. Placebo 20 mg/d subq	<u>Demographics at PRISM-1 entry:</u> <ul style="list-style-type: none"> • Age: 29.2 years • Female: 49.8% • White: 97.3% • Mean blood Phe: 1232.7 μmol/L 	PRISM-1 ITT: 261 Attrition: 48 (18.4%)	<u>Primary Endpoint:</u> Change from start of RDT to week 8 in blood Phe concentration 1&2 (pooled). 26.5 μmol/L 95% CI -68.3 to 121.3 3. 949.8 μmol/L 95% CI 760.4 to 1139.1	NA	<u>SAEs:</u> 1&2 (pooled). 3.0% 3&4 (pooled). 3.4% <u>AE causing study or study drug discontinuation:</u> 1&2 (pooled). 0%	NA for all	Risk of Bias (low/high/unclear): <u>Selection Bias:</u> High. Patients who could not titrate to or maintain a maintenance dose of pegvaliase in PRISM-1 were not included in PRISM-2 Part 2. Additionally, patients who did not achieve a blood Phe reduction of ≥20% (from mean of 2 consecutive blood Phe assessments) from treatment-naïve baseline

<p>DB, PC, 4 arm, discontinuation RCT</p> <p>PRISM-2 occurred immediately following PRISM-1 (Thomas, J et al⁹)</p>	<p>4. Placebo 40 mg/d subq</p> <p>8 weeks</p> <p>PRISM-2 occurred after PRISM-1 in which patients were titrated to a stable pegvaliase maintenance dosing regimen, so all patients had previously been on pegvaliase in Part 1 of PRISM-2.⁹</p>	<ul style="list-style-type: none"> Following Phe-restricted diet (>75% total protein intake from medical food): 15.7% <p><u>Demographics at PRISM-2 Part 2 entry:</u></p> <ul style="list-style-type: none"> Age: 30.9 years Female: 48.2% White: 98.2% Mean blood Phe: 520 µmol/L Following Phe-restricted diet (>75% total protein intake from medical food): 5.8% <p><u>Key Inclusion Criteria:</u></p> <ul style="list-style-type: none"> Age ≥18 years Diagnosis of PKU Received pegvaliase 20 mg/d or 40mg/d in Part 1 of PRISM-2 If receiving neuropsychiatric medications, required stable dose Willing & able to maintain stable protein intake DC of sapropterin (≥14 d) & large neutral amino acids (≥2 d) prior to 1st pegvaliase dose (requirement of PRISM-1⁹) <p><u>Key Exclusion Criteria (from PRISM-1⁹ unless noted):</u></p> <ul style="list-style-type: none"> Use of injectable medication 	<p>PRISM-2 Part 2 mITT*:</p> <p>Total: 86</p> <p>1. 29</p> <p>2. 29</p> <p>3. 14</p> <p>4. 14</p> <p><u>Attrition:</u></p> <p>Total: 14 (16.3%)</p> <p>1&2 (pooled). 9 (15.5%)</p> <p>3. 1 (7.1%)</p> <p>4. 4 (28.6%)</p>	<p>4. 664.8 µmol/L</p> <p>95% CI 465.5 to 864.1</p> <p>P<0.0001 for pooled 1&2 vs. each placebo group</p> <p>95% CI NR for comparative results</p> <p><u>Secondary Endpoints:</u></p> <p>Change from start of RDT to week 8 in ADHD RS-IV IA score for participants with baseline score >9:</p> <p>1&2 (pooled). 3.1</p> <p>3. -1.6</p> <p>4. 0.28</p> <p><u>LS mean change:</u></p> <p>1&2 (pooled) vs. 3: 4.7</p> <p>95% CI -0.19 to 9.5; p=0.06</p> <p>1&2 (pooled) vs. 4: 2.8</p> <p>95% CI -2.0 to 7.5; p=0.24</p> <p>Change from start of RDT to week 8 in ADHD RS-IV IA subscale score:</p> <p>1&2 (pooled). 1.2</p> <p>3. 0.74</p> <p>4. -0.40</p> <p><u>LS mean change:</u></p> <p>1&2 (pooled) vs. 3: 0.50</p> <p>95% CI -2.1 to 3.1; p=0.70</p> <p>1&2 (pooled) vs. 4: 1.6</p> <p>95% CI -1.2 to 4.5; p=0.25</p> <p>Change from start of RDT to week 8 in POMS score:</p> <p>1&2 (pooled). 4.2</p> <p>3. 7.2</p> <p>4. 0.19</p> <p><u>LS mean change:</u></p> <p>1&2 (pooled) vs. 3: -3.1</p> <p>95% CI -18.6 to 12.5; p=0.70</p> <p>1&2 (pooled) vs. 4: 4.0</p> <p>95% CI -12.6 to 20.5; p=0.63</p>	<p>NS</p> <p>NS</p> <p>NS</p> <p>NS</p> <p>NS</p> <p>NS</p>	<p>3&4 (pooled). 0%</p> <p><u>Hypersensitivity adverse events:</u></p> <p>1&2 (pooled). 39.4%</p> <p>3&4 (pooled). 13.8%</p> <p><u>Anaphylaxis:</u></p> <p>1&2 (pooled). 0%</p> <p>3&4 (pooled). 0%</p> <p><u>Generalized skin reaction >14 days:</u></p> <p>1&2 (pooled). 7%</p> <p>3&4 (pooled). 0%</p> <p><u>Injection site reaction:</u></p> <p>1&2 (pooled). 16%</p> <p>3&4 (pooled). 7%</p> <p>95% CI & p-values NR for all outcomes</p>	<p>at the time of RDT entry were not included in PRISM-2 Part 2 mITT analysis. Randomized 2:1 to current dose of pegvaliase or placebo by IWRS. Stratified by blood Phe and ADHD RS-IV IA subscale score. Baseline characteristics balanced.</p> <p><u>Performance Bias:</u> Low. Investigators, study staff, participants, and sponsor were blinded. Study drug self-injected subcutaneously. Matching placebo was used.</p> <p><u>Detection Bias:</u> Low. Investigators and study staff blinded. Many secondary outcomes are subjective. Raters were trained at each site in administering neuropsychiatric assessment tools.⁹</p> <p><u>Attrition Bias:</u> High. Attrition of 16.3% for PRISM-2 Part 2 eight week efficacy analysis, with high placebo attrition of 28.6%. Similar attrition in PRISM-1 (18.4%). Efficacy analysis based on mITT population of participants who had maintained pegvaliase dose from PRISM-2 Part 1 and had blood Phe reduction of ≥20% from treatment-naïve baseline at time of PRISM-2 Part 2 initiation. LOCF was used to impute data at monthly intervals for participants who terminated treatment early, which may lead to overestimation of efficacy results.⁹</p> <p><u>Reporting Bias:</u> Unclear. Protocol not available. Study funded by BioMarin Pharmaceutical Inc.</p> <p>Applicability:</p> <p><u>Patient:</u> All patients included in this trial had prior blood Phe reduction of ≥20% in PRISM-1. May not be applicable to patients who initially do not respond to pegvaliase or are initiating or titrating pegvaliase treatment. Included patients were limited to adults ≥18 years.</p> <p><u>Intervention:</u> Subq medication able to be self-administered. Doses match FDA labeled dosing options of 20 or 40 mg/d. Patients were not allowed to be on concomitant sapropterin or large neutral amino acids.</p>
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		<p>containing polyethylene glycol ≤ 3 months prior to screening</p> <ul style="list-style-type: none"> Patients pregnant, breastfeeding, or planning to become pregnant during study PRISM-2 Part 2: Unable to titrate to or maintain maintenance dose of pegvaliase in PRISM-1 		<p>Change from start of RDT to week 8 in PKU-POMS score: 1&2 (pooled). 2.1 3. 5.2 4. 2.0 <i>LS mean change:</i> 1&2 (pooled) vs. 3: -3.1 95% CI -10.3 to 4.1; p=0.40 1&2 (pooled) vs. 4: 0.08 95% CI -7.6 to 7.8; p=0.98</p>	<p>NS NS</p>		<p><u>Comparator:</u> Placebo appropriate for discontinuation trial. <u>Outcomes:</u> Blood Phe is a surrogate endpoint but commonly used in trials and accepted by the FDA as an appropriate PKU primary efficacy endpoint.¹⁰ Guidelines recommend maintaining blood Phe levels in certain ranges lifelong due to neuropsychiatric complications which can occur with elevated levels. Evaluating blood Phe levels in a discontinuation trial does not measure maximum effect of the drug. Many secondary outcomes are subjective. Duration of 8 weeks was relatively short. <u>Setting:</u> Study centers in the United States (number unspecified for PRISM-2 Part 2 specifically; 29 in PRISM-2).¹⁰</p>
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Abbreviations [alphabetical order]: ADHD RS-IV IA = Attention Deficit Hyperactivity Disorder Rating Scale IV inattention subscale; AE = adverse event; ARR = absolute risk reduction; CI = confidence interval; D = days; DB = double-blind; DC = discontinuation; ITT = intention to treat; IWRS = interactive web response system; LS = least squares; MC = multicenter; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not significant; PC = placebo controlled; PG = parallel-group; Phe = phenylalanine; PKU = phenylketonuria; POMS = Profile of Mood States score; PP = per protocol; RCT = randomized controlled trial; RDT = randomized discontinuation trial; SAE = serious adverse event; SUBQ = subcutaneously; U.S. = United States.

*mITT population included patients who had maintained their pegvaliase dose of 20 mg/day or 40 mg/day in Part 1 of PRISM-2 and had a blood Phe reduction of $\geq 20\%$ (from mean of 2 consecutive blood Phe assessments) from treatment-naïve baseline at the time of RDT entry. There were 39 patients identified in PRISM-2 Part 1 as being ineligible for PRISM-2 Part 2.⁹ These patients entered into PRISM-2 Part 4 after PRISM-1 Part 1.⁹

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PALYNZIQ safely and effectively. See full prescribing information for PALYNZIQ.

PALYNZIQ (pegvaliase-pqpz) injection, for subcutaneous use
Initial U.S. Approval: 2018

WARNING: RISK OF ANAPHYLAXIS

See full prescribing information for complete boxed warning.

- Anaphylaxis has been reported after administration of Palynziq and may occur at any time during treatment. (5.1)
- Administer the initial dose of Palynziq under the supervision of a healthcare provider equipped to manage anaphylaxis, and closely observe patients for at least 60 minutes following injection. Prior to self-injection, confirm patient competency with self-administration, and patient's and observer's (if applicable) ability to recognize signs and symptoms of anaphylaxis and to administer auto-injectable epinephrine, if needed. (2.4)
- Prescribe auto-injectable epinephrine. Prior to first dose, instruct the patient and observer (if applicable) on its appropriate use. Instruct the patient to seek immediate medical care upon its use. Instruct patients to carry auto-injectable epinephrine with them at all times during Palynziq treatment. (2.4, 5.1)
- Palynziq is available only through a restricted program called the Palynziq REMS. (5.2)

INDICATIONS AND USAGE

Palynziq is a phenylalanine-metabolizing enzyme indicated to reduce blood phenylalanine concentrations in adult patients with phenylketonuria who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management. (1)

DOSAGE AND ADMINISTRATION

Dosage (2.1)

- Obtain baseline blood phenylalanine concentration before initiating treatment.
- The recommended initial dosage is 2.5 mg subcutaneously once weekly for 4 weeks.
- Titrate the dosage in a step-wise manner over at least 5 weeks based on tolerability to achieve a dosage of 20 mg subcutaneously once daily. See full prescribing information for titration regimen.
- Assess patient tolerability, blood phenylalanine concentration, and dietary protein and phenylalanine intake throughout treatment.
- Consider increasing the dosage to a maximum of 40 mg subcutaneously once daily in patients who have been on 20 mg once daily continuously for at least 24 weeks and who have not achieved either a 20% reduction in blood phenylalanine concentration from pre-treatment baseline or a blood phenylalanine concentration less than or equal to 600 micromol/L.
- Discontinue Palynziq in patients who have not achieved at least a 20% reduction in blood phenylalanine concentration from pre-treatment baseline or a blood phenylalanine concentration less than or equal to

600 micromol/L after 16 weeks of continuous treatment with the maximum dosage of 40 mg once daily.

- Reduce the dosage and/or modify dietary protein and phenylalanine intake, as needed, to maintain blood phenylalanine concentrations within a clinically acceptable range and above 30 micromol/L.

Blood Phenylalanine Monitoring and Diet (2.2)

- Obtain blood phenylalanine concentrations every 4 weeks until a maintenance dosage is established.
- After a maintenance dosage is established, periodically monitor blood phenylalanine concentrations.
- Counsel patients to monitor dietary protein and phenylalanine intake, and adjust as directed by their healthcare provider.

Premedication (2.3, 5.1, 5.3)

- Consider premedication for hypersensitivity reactions.

Administration Instructions (2.4)

- Rotate injection sites. If more than one injection is needed for a single dose, the injection sites should be at least 2 inches away from each other.

DOSAGE FORMS AND STRENGTHS

Injection: 2.5 mg/0.5 mL, 10 mg/0.5 mL, and 20 mg/mL in a single-dose prefilled syringe. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions, Other than Anaphylaxis: Management should be based on the severity of the reaction, recurrence, and clinical judgement, and may include dosage adjustment, temporary drug interruption, or treatment with antihistamines, antipyretics, and/or corticosteroids. (5.3)

ADVERSE REACTIONS

Most common adverse reactions (at least 20% in either treatment phase) are: injection site reactions, arthralgia, hypersensitivity reactions, headache, generalized skin reactions lasting at least 14 days, pruritus, nausea, abdominal pain, oropharyngeal pain, vomiting, cough, diarrhea, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact BioMarin Pharmaceutical Inc. at 1-866-906-6100, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Effect of Palynziq on Other PEGylated Products: Monitor for hypersensitivity reactions, including anaphylaxis, with concomitant treatment. (7.1)

USE IN SPECIFIC POPULATIONS

Pregnancy: May cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2018

Appendix 2: Proposed Prior Authorization Criteria

Phenylketonuria Sapropterin

Goal(s):

- Promote safe and cost effective therapy for the treatment of phenylketonuria.

Length of Authorization:

- Initial: 1 to 92 months;
- Renewal: 16 weeks to 1 year

Requires PA:

- Sapropterin and pegvaliase (pharmacy and physician administered claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated and is the requested treatment funded by the OHP for that condition <u>Is the diagnosis funded by OHP?</u> Note: Treatments which appear on an unfunded line of the prioritized list are not funded by the OHP	Yes: Go to #2	No: Pass to RPh. Deny; not funded by OHP
2. Is the request for renewal of therapy previously approved by the FFS system?	Yes: Go to Renewal Criteria	No: Go to #3
3. Is the drug prescribed by or in consultation with a specialist in metabolic disorders?	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness
4. <u>Is the request for sapropterin?</u>	Yes: <u>Go to #5</u>	No: <u>Go to #8</u>

Approval Criteria		
4.5. Is the diagnosis tetrahydrobiopterin- (BH4-) responsive phenylketonuria?	Yes: Go to #65	No: Pass to RPh. Deny; medical appropriateness
5.6. Is the patient currently compliant with a Phe-restricted diet and unable to achieve target blood phenylalanine level?	Yes: Go to #76	No: Pass to RPh. Deny and recommend Phe-restricted diet.
6.7. Is the patient's baseline blood phenylalanine level provided in the request and above the target range (see Clinical Notes)?	Yes: Approve for 2 months if initial dose is 5-10 mg/kg/day (to allow for titration to 20 mg/kg/day). Approve for 1 month if initial dose is 20 mg/kg/day (adults and children).	No: Request information from provider.
8. Is the request for pegvaliase?	Yes: Go to #9	No: Pass to RPh. Deny; medical appropriateness
9. Is the patient 18 years of age or older with a diagnosis of phenylketonuria?	Yes: Go to #10	No: Pass to RPh. Deny; medical appropriateness
10. Is the patient's blood phenylalanine concentration documented in the request and greater than 600 $\mu\text{mol/L}$ on existing management (such as dietary phenylalanine restriction or sapropterin)?	Yes: Approve for 9 months based on FDA-approved induction, titration, and maintenance dosing*	No: Pass to RPh. Deny; medical appropriateness. If not documented, request information from provider.

Renewal Criteria		
1. Is the request for sapropterin?	Yes: Go to #2	No: Go to #4

Renewal Criteria		
<u>2. Did the patient meet the target phenylalanine level set by the specialist (see Clinical Notes)?</u>	<u>Yes: Go to #2</u>	<u>No: Pass to RPh. Deny for lack of treatment response.</u>
<u>3. Is the patient remaining compliant with the Phe-restricted diet?</u>	<u>Yes: Approve for 12 months</u>	<u>No: Pass to RPh. Deny and recommend Phe-restricted diet.</u>
<u>4. Is the request for pegvaliase?</u>	<u>Yes: Go to #5</u>	<u>No: Pass to RPh. Deny; medical appropriateness</u>
<u>5. Has there been a reduction from baseline phenylalanine concentration of 20% or greater?</u>	<u>Yes: Approve for 12 months</u>	<u>No: Go to #6</u>
<u>6. Has there been a reduction in blood phenylalanine concentration to less than or equal to 600 µmol/L?</u>	<u>Yes: Approve for 12 months</u>	<u>No: Go to #7</u>
<u>7. Is the request for a first renewal of pegvaliase therapy and the patient had been on pegvaliase 20 mg daily for at least 24 weeks?</u>	<u>Yes: Approve for 16 weeks for trial of maximum dose of 40 mg once daily. Continued approval at this dose requires documentation of improvement (>20% reduction from baseline or less than 600 µmol/L in phenylalanine concentration).</u>	<u>No: Pass to RPh. Deny for lack of treatment response.</u>

Clinical Notes:

Target blood phenylalanine levels in the range of 120-360 µmol/L for patients in all age ranges.¹

In addition to the recommended Phe concentrations, a 30% or more reduction in blood Phe is often considered a clinically significant change from baseline and should occur after the initial trial.² If not, the patient is a non-responder and will not benefit from sapropterin therapy.

Sapropterin dDoses above 20 mg/kg/day have not been studied in clinical trials.

***Pegvaliase FDA-Recommended Dosage and Administration:**

<u>Treatment</u>	<u>Pegvaliase Dosage</u>	<u>Duration*</u>
<u>Induction</u>	<u>2.5 mg once weekly</u>	<u>4 weeks</u>
<u>Titration</u>	<u>2.5 mg twice weekly</u>	<u>1 week</u>
	<u>10 mg once weekly</u>	<u>1 week</u>
	<u>10 mg twice weekly</u>	<u>1 week</u>
	<u>10 mg four times per week</u>	<u>1 week</u>
	<u>10 mg once daily</u>	<u>1 week</u>
<u>Maintenance</u>	<u>20 mg once daily</u>	<u>24 weeks</u>
<u>Maximum**</u>	<u>40 mg once daily</u>	<u>16 weeks***</u>

*Additional time may be required prior to each dosage escalation based on patient tolerability.

**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 (>20% reduction in blood phenylalanine concentration from pre-treatment baseline or a blood phenylalanine concentration <600 µmol/L) with 20 mg once daily continuous treatment for at least 24 weeks.

***Discontinue pegvaliase treatment in patients who have not achieved a response (>20% reduction in blood phenylalanine 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.

References:

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2. Blau N., Belanger-Quintana A., Demirkol M. Optimizing the use of sapropterin (BH₄) in the management of phenylketonuria. *Molecular Genetics and Metabolism* 2009;96:158-163.

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Implementation: TBD; 8/16; 1/1/14