PDL DRUG REVIEW

Proprietary Name: Palynziq®
Common Name: pegvaliase-pqpz
PDL Category: Phenylketonuria

Summary

Pharmacology/Usage: Pegvaliase-pqpz, the active ingredient of Palynziq®, is a phenylalanine-metabolizing enzyme that is composed of recombinant phenylalanine ammonia lyase (rAvPAL) conjugated to N-hydroxysuccinimide (NHS)-methoxypolyethylene glycol (PEG). It is a PEGylated phenylalanine ammonia lyase (PAL) enzyme that converts phenylalanine to ammonia and *trans*-cinnamic acid. It substitutes for the deficient phenylalanine hydroxylase (PAH) enzyme activity in patients with phenylketonuria (PKU) and reduces blood phenylalanine concentrations. Treatment of adults with PKU resulted in the reduction of blood phenylalanine concentrations from pre-treatment baseline.

Indication: To reduce blood phenylalanine concentrations in adult patients with phenylketonuria (PKU) who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management.

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings in studies of pregnant animals without PKU, treatment may cause fetal harm when administered to a pregnant woman. Limited available data with use in pregnant women are not sufficient to inform a drug-associated risk of adverse developmental outcomes. There are risks to the fetus associated with poorly controlled phenylalanine concentrations in women with PKU during pregnancy. Advise pregnant women of the potential risks to the fetus. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Colorless to pale yellow solution for injection: 2.5mg/0.5ml, 10mg/0.5ml, and 20mg/ml in single-dose prefilled syringe. Store in refrigeration; once stored at room temperature, do not return the product to the refrigerator.

Recommended Dosage: Treatment with Palynziq® should be managed by a healthcare provider experienced in the management of PKU. It is recommended to obtain baseline blood phenylalanine concentration before starting treatment. Prior to the first dose, an auto-injectable epinephrine should be prescribed to the patient due to risk of anaphylaxis.

The recommended initial induction dose is 2.5mg SC once weekly for 4 weeks. Administer the initial dose under the supervision of a healthcare provider. Titrate the dose in a step-wise manner, based on tolerability, over at least 5 weeks, to achieve a dose of 20mg SC once daily (refer to the prescribing information for additional information regarding the recommended dosing regimen). The recommended injection sites are the front middle of thighs and the abdomen at least 2 inches away from the navel. If a caregiver is giving the injection, the top of the buttocks and the back of the upper arms are also appropriate injection sites. Rotate sites for SC injections.

For maintenance, therapeutic response may not be achieved until the patient is titrated to an effective maintenance dose of Palynziq®. Use the lowest effective and tolerated dose of Palynziq®. Assess patient tolerability, blood phenylalanine concentrations, and dietary protein and phenylalanine intake throughout

treatment. Maintain the Palynziq® dosage at 20mg SC QD for at least 24 weeks, and consider increasing to a maximum of 40mg SC QD in patients who have been maintained continuously on 20mg QD 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 ≤600micromol/L.

Discontinue treatment in patients who have not achieved a response (at least a 20% reduction in blood phenylalanine concentration from pre-treatment baseline or a blood phenylalanine concentration ≤600micromol/L) after 16 weeks of continuous treatment with the maximum dosage of 40mg QD.

After starting treatment, obtain blood phenylalanine concentrations every 4 weeks until a maintenance dose is established. After this is established, periodic blood phenylalanine monitoring is recommended to assess blood phenylalanine control. In addition, monitor that patients' dietary protein and phenylalanine intake through treatment and counsel on how to adjust their dietary intake, as needed, based on blood phenylalanine concentrations.

For hypersensitivity reactions, consider premedication with an H1-receptor antagonist, H2-receptor antagonist, and/or antipyretic prior to Palynziq® administration based on individual patient tolerability.

Drug Interactions: In clinical trials, most patients developed anti-PEG IgM and IgG antibodies after treatment with Palynziq®. While the clinical effects of concomitant treatment with different PEGylated products is not known, it is recommended to monitor patients treated with Palynziq® and concomitantly with other PEGylated products for hypersensitivity reactions, including anaphylaxis.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Palynziq®) during the induction/titration phase and during the maintenance phase. There was no placebo data to compare with.* The most frequently reported adverse events included injection site reactions (88%, 72%), arthralgia (74%, 61%), hypersensitivity reactions (53%, 61%), headache (35%, 50%), generalized skin reaction lasting at least 14 days (21%, 37%), pruritus (20%, 24%), nausea (18%, 26%), dizziness (16%, 17%), abdominal pain (14%, 25%), oropharyngeal pain (13%, 23%), fatigue (13%, 22%), vomiting (13%, 26%), cough (9%, 22%), diarrhea (9%, 22%), anxiety (5%, 18%), alopecia (5%, 17%), and nasal congestion (4%, 18%).

Palynziq® has a box warning regarding the increased risk of anaphylaxis, which has been reported after use and may occur at any time during treatment. The initial dose must be administered under the supervision of a healthcare provider equipped to manage anaphylaxis, and closely watch the patient for at least 60 minutes after injection. Consider having an adult observer for patients who may need assistance in recognizing and managing anaphylaxis during treatment. The warning adds that auto-injectable epinephrine should be prescribed to all patients treated with Palynziq®. Prior to the first treatment, instruct the patient on how to recognize the signs and symptoms of anaphylaxis, how to properly administer the epinephrine and to seek medical care immediately. Consider the risks and benefits of re-administering Palynziq® after an episode of anaphylaxis. The box warning states that due to the risk of anaphylaxis, Palynziq® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Palynziq® REMS.

Requirements of the Palynziq® REMS include that the prescribers must be certified with the program by enrolling in the program and completing training, the prescribers must prescribe auto-injectable epinephrine with Palynziq®, pharmacies must be certified and dispense only to authorized patients, patients must enroll in the program and be educated about the risk of anaphylaxis, and the patient must have the auto-injectable epinephrine available at all times while taking Palynziq®.

Contraindications: There are no contraindications listed with this product.

Manufacturer: BioMarin Pharmaceutical Inc

Analysis: *Study 301* was an open-label, randomized, multicenter study that included adults with PKU to assess the safety and tolerability of self-administered Palynziq® in an induction/titration/maintenance regimen with a target

maintenance dose of 20mg SC QD or 40mg SC QD. At treatment initiation, patients demonstrated inadequate blood phenylalanine control on existing management (blood phenylalanine concentration >600micromol/L; N=253), and 8 had blood phenylalanine concentrations ≤600micromol/L. Existing management options included prior or current restriction of dietary phenylalanine and protein intake, and/or prior treatment with sapropterin dihydrochloride.

The 261 patients enrolled were 16 to 55 years of age and had a baseline mean blood phenylalanine of 1,233 micromol/L. Patients were randomized to one of 2 target maintenance dose arms and were titrated to reach their target dosage. Of these patients, 195 (75%) reached their randomized maintenance dosage (103 in the 20mg arm and 92 in the 40mg arm). Of those who reached the maintenance dosage, patients in the 20mg arm reached it at a median time of 10 weeks, and patients in the 40mg arm reached it at a median of 11 weeks. Of the 261 patients enrolled in Study 301, 54 discontinued treatment during the study, 4 completed the study and did not continue to Study 302), 152 continued to the eligibility period of Study 302, and 51 continued directly from Study 301 into the long-term treatment period of Study 302.

Study 302 was an efficacy trial that included 152 patients from Study 301 and 12 patients from other Palynziq® clinical trials. Patients enrolled in Study 302 and continued treatment with Palynziq® in Study 302 for up to 13 weeks to assess eligibility for randomized withdrawal period. Following this period of up to 13 weeks of additional treatment in Study 302, eligibility for entry into the efficacy assessment period (randomized withdrawal period) was determined by whether a patient achieved at least a 20% reduction in blood phenylalanine concentration from pre-treatment baseline (when in previous studies). Eighty-six out of 164 patients (52%) met this response target and continued into the randomized withdrawal period.

In the double-blind, placebo-controlled, randomized withdrawal period, patients were randomized to either continue their maintenance Palynziq® dose or to receive matching placebo for a total of 8 weeks. The treatment difference in least squares mean change in blood phenylalanine concentration from the Study 302 randomized withdrawal baseline to randomized withdrawal week 8 for each treatment arm was the primary endpoint, and can be seen in the table below, which was adapted from the prescribing information. At Study 302 randomized withdrawal week 8, Palynziq®-treated patients maintained their blood phenylalanine concentrations as compared to their randomized withdrawal baseline, but those randomized to placebo returned to their pre-treatment baseline blood phenylalanine concentrations.

	Blood Phenylalanine Concentration (micromol/L) mean			LS mean change	Treatment difference
	Pre-Treatment baseline	Study 302 randomized withdrawal baseline	Study 302 randomized withdrawal week 8		
Palynziq® 20mg QD	1450.2	596.8 (N=29)	553.0 (N=26) ^	-23.3	-973.0; p<0.0001
Placebo 20mg QD	1459.1	563.9 (N=14)	1509.0 (N=13) ^	949.8	
Palynziq® 40mg QD	1185.8	410.9 (N=29)	566.3 (N=23) ^	76.3	-588.5; p<0.0001
Placebo 40mg QD	1108.9	508.2 (N=14)	1164.4 (N=10) ^	664.8	

^Patients who did not complete phenylalanine assessment within the window for week 8 (day 43 to 56) were excluded

Study 301 and 302 Continuous Treatment: Of the 118 patients from Study 301 with pre-treatment baseline blood phenylalanine concentration >600micromol/L who were randomized to and received at least one dose of 20mg QD, 108 patients, 98 patients, and 51 patients were treated for at least 24 weeks, 48 weeks, and 96 weeks, respectively. Of the 118 patients, 53 reached their first response (at least a 20% reduction in blood phenylalanine concentration from pre-treatment baseline or a blood phenylalanine concentration ≤600 micromol/L) by 4 weeks of treatment with 20mg QD and 28 patients reached their first response between weeks 4 and 24 with 20mg daily. Of the 118 patients, 25 patients escalated their dose from 20mg to 40mg QD before reaching a first response. Of these 25 patients, 8 reached their first response by 4 weeks of treatment with 40mg and 6 patients reached their first response between weeks 4 and 16 with 40mg.

Place in Therapy: Palynziq® is a subcutaneous injection indicated to reduce blood phenylalanine concentrations in adults with PKU who have uncontrolled blood phenylalanine concentrations greater than 600micromol/L on existing management.

There is no evidence that Palynziq® is safer or more effective than the currently available medications. It is therefore recommended that Palynziq® remain non-preferred to ensure it is used in clinically appropriate situations.

PDL Placement:
- ☐ **Preferred**
- ☒ **Non-Preferred**

References

[1] Palynziq® [package insert]. Novato, CA: BioMarin Pharmaceutical, Inc; 2018.

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