Palynziq (pegvaliase-pqpzl)

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This medical policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the Palynziq (pegvaliase-pqpzl) Policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines and clinical studies.

Palynziq (pegvaliase-pqpzl) is a PEGylated phenylalanine ammonia lyase (PAL) enzyme that converts phenylalanine to ammonia and trans-cinnamic acid, thereby reducing blood phenylalanine concentrations. Palynziq is indicated to reduce blood phenylalanine concentrations in adult patients with phenylketonuria (PKU) who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L (µmol/L) on existing management.

POLICY

Required Documentation

The following information is necessary to initiate the prior authorization review:

1. Submission of medical records (e.g., chart notes, laboratory values) documenting that the patient has a baseline blood phenylalanine concentration greater than 600 micromol/L despite dietary phenylalanine-restricted diet and Kuvan
2. Submission of medical records (e.g., chart notes, laboratory values) documenting response to therapy defined in continuation criteria with blood phenylalanine concentrations

3. Submission of medical records (e.g., chart notes, laboratory values) documenting that the patient is not receiving Palynziq in combination with Kuvan (sapropterin dihydrochloride) or will be discontinued after an appropriate period of overlap.

Criteria for Initial Approval

I. Palynziq (pegvaliase-pqpzl) may be considered **medically necessary** for the treatment of phenylketonuria (PKU) when the following criteria are met:
   - Must have a diagnosis of phenylketonuria
   - Must be ≥ 18 years of age
   - Must be prescribed by or in consultation with a healthcare provider experienced in the management of PKU
   - Must have documentation of elevated blood phenylalanine level (> 600 µmol/L) for 6 months prior to treatment despite existing management (i.e., restriction of dietary phenylalanine and protein intake)
   - Treatment with Kuvan (sapropterin dihydrochloride) was ineffective, not tolerated, is contraindicated, or patient has two null mutations in *trans*
   - Patient will not be receiving Palynziq in combination with Kuvan (sapropterin dihydrochloride) or will be discontinued after an appropriate period of overlap.
   - Patient will be prescribed auto-injectable epinephrine due to the risk of anaphylaxis with Palynziq use

Approval will be for **6 months**

Continuation of Therapy

I. Palynziq (pegvaliase-pqpzl) may be considered medically necessary for continued treatment of PKU when the following criteria are met:
   - Patient has achieved a clinical response to Palynziq treatment as evidenced by a blood phenylalanine concentration less than or equal to 600 micromol/L
   - Patient has demonstrated an improvement or stabilization in clinical status (e.g., neurocognitive and/or neuropsychiatric function)
   - Patient is not receiving Palynziq in combination with Kuvan (sapropterin dihydrochloride)

Approval will be for **12 months**

OR

- The patient has not achieved a clinical response to treatment with Palynziq (blood phenylalanine concentration less than or equal to 600 µmol/L) and meets one of the following requirements:
  - Patient has not been titrated to the maximum allowed dose of 60mg once daily
  - Patient has received less than 16 weeks of continuous treatment at the maximum allowed dose
- Patient is not receiving Palynziq in combination with Kuvan (sapropterin dihydrochloride) or will be discontinued after an appropriate period of overlap.

Approval will be for **6 months** when titrating dose to 60 mg/day

Dosage and Administration

Medication	FDA-recommended dosing
Palynziq (pegvaliase-pqpz) 2.5 mg/0.5 mL single-dose prefilled syringe for subcutaneous injection	Induction: 2.5 mg once weekly for 4 weeks. Titration: 2.5 mg twice weekly for 1 week, 10 mg once weekly for 1 week, 10 mg twice weekly for 1 week, 10 mg four times per week for 1 week, 10 mg once daily for 1 week. Maintenance: 20 mg once daily, or 40 mg once daily Maximum: 60 mg once daily Discontinue: Patients who have not achieved a response after 16 weeks of continuous treatment with the maximum dosage of 60 mg once daily.
Palynziq (pegvaliase-pqpz) 10 mg/0.5 mL single-dose prefilled syringe for subcutaneous injection	
Palynziq (pegvaliase-pqpz) 20 mg/mL single-dose prefilled syringe for subcutaneous injection	

CLINICAL RATIONALE

Phenylketonuria (PKU) is a rare genetic disorder where an enzyme deficiency results in an inability or reduced ability to metabolize the amino acid phenylalanine (Phe) into tyrosine. This deficiency causes an increase in Phe concentrations in the blood and brain thereby causing brain abnormalities and cognitive impairment. The toxic effects of Phe can be minimized by a low Phe diet begun when diagnosed in infancy. Those with severe forms of PKU will require a diet composed primarily of medical food as their primary source of protein equivalents (estimated 6 g of natural protein intake is typically allowed in PKU patients with severe disease) where individuals with mild or moderate PKU will need less medical food and/or modified low-protein food to maintain blood Phe control. Neurocognitive and psychiatric symptoms can develop later in life when it is more difficult to maintain Phe control, and a correlation has been reported between improved cognitive performance and maintaining control of blood Phe into adulthood. However, long-term cognitive outcomes in adult PKU patients is unclear as there is inconsistent evidence demonstrating if there are benefits in neurocognitive function and neuropsychiatric effects when lower Phe levels is continued throughout adulthood.

Practice guidelines issued by the American College of Medical Genetics and Genomics (ACMG) support the need for lifelong management of Phe levels in patients with phenylketonuria (PKU) as it is essential to optimize functioning of individuals with PAH deficiency. While intellectual disability does not appear to occur in patients who are well controlled in infancy and childhood, a variety of adverse neurocognitive and psychiatric outcomes, including deficits in executive function and psychiatric symptoms such as anxiety, depression, and phobias can develop later in life when there is relaxation of Phe control. These later effects can be disabling and can result in a lower overall level of educational attainment and socioeconomic status per ACMG. Historically, liberalization of the PHE-restricted diet and relaxation Phe control was allowed. As more information has accumulated regarding effects of elevated Phe levels on brain function, this practice is no longer acceptable. The guideline states that the treatment goal for PKU patients of all ages should be blood levels of phenylalanine (Phe) between 120-360 umol/L and that a reduction of blood Phe, increase in dietary Phe tolerance, or improvement in clinical symptoms are all valid indications for the continuation of therapy.

Palynziq (pegvaliase-pqpz) is the first biologic therapy approved for the treatment of PKU and is indicated for the treatment of adult patients who have uncontrolled blood Phe concentrations > 600 µmol/L on existing

management. In patients who require treatment with the maximum maintenance dose of Palynziq (pegvaliase-pqpz) 60 mg daily, titration may take up to 33 weeks.

The efficacy of Palynziq (pegvaliase-pqpz) was evaluated in two phase III trials, PRISM-1 and PRISM-2. Patients received induction dosing and titration up to a maintenance dose of Palynziq (pegvaliase-pqpz) in the PRISM-1 trial, while PRISM-2 included a pivotal portion that evaluated the effect of therapy discontinuation. PRISM-2 is a continuation of PRISM-1, where a subset of patients who completed PRISM-1 enrolled in PRISM-2. Blood Phe, safety, and neuropsychiatric assessments were conducted during both trials.

PRISM-1 was an open-label, multicenter, randomized, parallel-group phase III trial. Palynziq (pegvaliase-pqpz)-naïve adult patients with PKU (N = 261) and a blood Phe concentration of > 600 µmol/L for 6 months prior to enrollment were randomized to receive Palynziq (pegvaliase-pqpz) up to a maintenance dose of 20 mg/day (n = 131) or 40 mg/day (n = 130). Of the 261 patients who enrolled and received treatment with Palynziq (pegvaliase-pqpz) in PRISM-1, 72% and 33% of patients received treatment for ≥ 12 months and ≥ 24 months, respectively. The mean blood Phe concentration decreased by 51% from baseline (n = 164) and 69% from baseline (n = 51) at 12 months and 24 months, respectively. Kaplan-Meier analyses of time to blood Phe thresholds estimated that 44% of patients (95% confidence interval [CI] 38 to 50) and 61% of patients (95% CI 54 to 67) achieved blood Phe reduction to ≤ 360 µmol/L at 12 months and 24 months, respectively. An estimated 51% of patients (95% CI 45 to 58) achieved a reduction of blood Phe concentration to ≤ 120 µmol/L at 24 months. An estimated 72% of patients (95% CI 66 to 77) and 78% of patients (95% CI 73 to 83) achieved ≥ 20% reduction in blood Phe from baseline at 12 months and 24 months, respectively.

Changes in attention and mood symptoms were evaluated using the Attention Deficit Hyperactivity Disorder Rating Scale IV inattention (ADHD RS-IV IA) subscale and the Profile of Mood States (POMS) scale, including a PKU-specific POMS (PKU-POMS) developed for the PRISM trials. These secondary efficacy measures were added to the PRISM trials during a protocol change. A decline in mean ADHD RS-IV IA subscale score was observed at 12 months (4.7-point decline from baseline score of 9.8; n = 253 at baseline and n = 178 at 12 months) and at 24 months (6.4-point decline from baseline; n = 89 at 24 months). Patients with a baseline ADHD RS-IV IA subscale score > 9 had a larger magnitude of change from baseline in ADHD RS-IV IA subscale scores. Decreases from baseline in mean POMS score, PKU-POMS score and PKU-POMS confusion subscale score were also observed at 12 months and 24 months. Data showed a correlation between improved neuropsychiatric symptoms and improvement of blood Phe control but no analysis of clinical or statistical significance was provided for the neuropsychiatric assessments.

PRISM-2 is a phase III trial consisting of four parts: part 1 was an open-label period to assess eligibility of patients (the majority of whom were from PRISM-1) to enter part 2, part 2 was a double-blind, placebo-controlled, 8-week randomized discontinuation trial, part 3 is an open-label period of pharmacodynamic and pharmacokinetic analyses, and part 4 is an open-label extension. The randomized discontinuation trial in PRISM-2 part 2 enrolled patients (n=86) 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. 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). 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). However, a decline in neuropsychiatric or neurocognitive symptoms as a result of discontinuation of Palynziq was not observed.

The most common adverse events reported in the Palynziq (pegvaliase-pqpz) trials included injection site reactions, arthralgia, hypersensitivity reactions, and headache. Anaphylaxis occurred in roughly one in ten patients. Because of the risk of anaphylaxis, Palynziq (pegvaliase-pqpz) is available only through a restricted distribution program. The Palynziq REMS requires prescribers, patients, and dispensing pharmacies to be certified by or enrolled in the program by completing enrollment and assessment forms acknowledging that they understand the risk of anaphylaxis associated with the use of Palynziq (pegvaliase-pqpz) and agree to comply with program requirements. Prescribers must prescribe auto-injectable epinephrine with Palynziq (pegvaliase-pqpz), and patients must have auto-injectable epinephrine available at all times while receiving Palynziq (pegvaliase-pqpz). Patients must also be counseled on how to recognize and respond to signs and symptoms of anaphylaxis.

A sub analysis from the PRISM-1 and PRISM-2 studies assessed the immunogenicity of Palynziq treatment in adults with PKU and the impact it has on safety and efficacy. The results found that patients with Palynziq developed antidrug antibody responses that matured to a clinical non-responsive state over time, allowing substantial and sustained blood Phe reduction to be achieved with a manageable safety profile for most patients. The key is to introduce Palynziq slowly with incremental dose increases to allow the immune system to stabilize although there is insufficient evidence to determine if any subgroup would be more at risk for anaphylaxis when beginning treatment with Palynziq.

The FDA approved a label expansion that increased the maximum allowable dose for Palynziq to 60 mg in early October 2020. This approval was due to results from the Phase 3 PRISM studies showing 19% of study participants required a 60 mg dose to achieve an adequate response to Palynziq. The open-label extension study followed approximately 40 patients from prior trials who received Palynziq at doses greater than 40 mg a day. Irrespective of the dose used, Palynziq lowered phenylalanine to target levels in two thirds (66%) of the 86 patients who received treatment for at least two years. Among those treated for three years, 66% also reached phenylalanine concentrations of 360 umol/L or lower. Of the patients who achieved their first response at a dose of 60 mg once daily, a 67% did so within 16 weeks of treatment. Safety data from patients followed for more than six years in the open-label trial also showed that Palynziq's safety profile was consistent with previous studies, irrespective of the dose. The rate and types of adverse events were similar among patients receiving 20 mg, 40 mg, and 60 mg.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

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POLICY HISTORY

Policy #: 05.02.63
Reviewed: February 2022
Revised: October 2021
Current Effective Date: October 20, 2021