Phenylketonuria Prior Authorization Program Summary

This prior authorization program applies to Commercial, NetResults A series, SourceRx and Health Insurance Marketplace formularies.

OBJECTIVE
The intent of the Phenylketonuria Prior Authorization (PA) program is to appropriately select patients for treatment according to product labeling and/or clinical studies and/or clinical practice guidelines.

TARGET DRUGS
Kuvan® (sapropterin)
Palynziq™ (pegvaliase-pqpz)

Brand (generic)	GPI	Multisource Code
Kuvan (sapropterin)		
100 mg tablet	30908565107320	M, N, O, or Y
100 mg powder	30908565103020	M, N, O, or Y
500 mg powder	30908565103040	M, N, O, or Y
Palynziq (pegvaliase-pqpz)		
2.5 mg/0.5 mL syringe	3090855040E510	M, N, O, or Y
10 mg/0.5 mL syringe	3090855040E520	M, N, O, or Y
20 mg/1 mL syringe	3090855040E530	M, N, O, or Y

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
INITIAL EVALUATION
The requested agent will be approved for initial use when ALL of the following are met:

1. The patient has a diagnosis of phenylketonuria (PKU)
   AND
2. The patient is on a phenylalanine (Phe) restricted diet
   AND
3. The prescriber has submitted a baseline blood Phe level measured prior to initiation of the requested agent which is above the recommended levels [all ages: 2-6 mg/dL (120-360 mcmol/L)]
   AND
4. The prescriber is a specialist with knowledge and expertise in metabolic diseases or genetic diseases or has consulted with a specialist in metabolic or genetic diseases
   AND
5. The patient does not have any FDA labeled contraindication(s) to the requested agent
   AND
6. The dose is within the FDA-labeling

Length of Approval: Up to 6 months unless otherwise noted below:

- **Kuvan (sapropterin):** Approve for 2 months if initial dose is 5 mg/kg/day to <20 mg/kg/day and for 1 month if initial dose is 20 mg/kg/day
- **Palynziq**: 6 months

RENEWAL EVALUATION

The requested agent will be approved for renewal when ALL of the following are met:

1. The patient was previously approved for therapy with the requested agent through the Prime Therapeutics PA process
   AND
2. The patient has been successfully treated with the requested agent as defined by one of the following**:**
   a. The patient's blood Phe levels are being maintained within the acceptable range [all ages: 2-6 mg/dL (120-360 mcmol/L)]
      OR
   b. The patient has had a ≥30% decrease in blood Phe level from baseline
   AND
3. The patient is on a phenylalanine (Phe) restricted diet
   AND
4. The prescriber is a specialist with knowledge and expertise in metabolic diseases or genetic diseases or has consulted with a specialist in metabolic or genetic diseases
   AND
5. The patient does not have any FDA labeled contraindication(s) to the requested agent
   AND
6. The dose is within the FDA-labeling

Length of Approval: 12 months

FDA APPROVED INDICATIONS AND DOSAGE[1,14]

<table>
<tr><th>Agent</th><th>Indication</th><th>Dose*</th></tr>
<tr><td>Kuvan®
(sapropterin)</td><td>Reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin-(BH4-) responsive phenylketonuria (PKU).</td><td>Patients 1 month to 6 years: 10 mg/kg once daily

Patients 7 years and older: 10 to 20 mg/kg once daily</td></tr>
<tr><td>Palynziq™
(pegvalise-pqpz)

subcutaneous injection</td><td>To reduce blood phenylalanine concentrations in adult patients with phenylketonuria who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management</td><td>Induction: 2.5 mg once weekly for 4 weeks

Titration: based on tolerability over at least 5 weeks to achieve 20 mg once daily

<table>
<tr><th></th><th>Dose</th><th>Duration</th></tr>
<tr><td>Titration</td><td>2.5 mg twice weekly</td><td>1 week</td></tr>
<tr><td></td><td>10 mg once weekly</td><td>1 week</td></tr>
<tr><td></td><td>10 mg twice weekly</td><td>1 week</td></tr>
<tr><td></td><td>10 mg four times per week</td><td>1 week</td></tr>
<tr><td></td><td>10 mg once daily</td><td>1 week</td></tr>
<tr><td>Maintenance</td><td>20 mg once daily</td><td>24 weeks</td></tr>
<tr><td>Maximum</td><td>40 mg once daily</td><td></td></tr>
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* Dose adjustment: Dose of Kuvan may be adjusted in the range of 5 to 20 mg/kg once daily

CLINICAL RATIONALE

Phenylketonuria (PKU) is caused by a deficiency of the enzyme phenylalanine hydroxylase (PAH).[2] This enzyme deficiency impairs metabolism of phenylalanine (Phe) and results in hyperphenylalaninemia (HPA).[2] When untreated, HPA is neurotoxic and can lead to profound neurocognitive and developmental defects.[3] Genetic screening for PKU is done in all 50 states, and the estimated incidence is one case in 15,000 newborns.[2]

The mainstay of therapy in PKU is dietary restriction of phenylalanine.[13] This requires the use of medical foods including phenylalanine-free protein substitutes. In infants with PKU, breastfeeding alternated with phenylalanine free formula is recommended. The Phe restricted diet should be continued indefinitely.[2] Maintaining compliance with dietary restrictions is

difficult, especially in children and adolescents, due to poor palatability and strict requirements.[3,4] According to the American College of Medical Genetics and Genomics (ACMG) and Genetic Metabolic Dieticians (GMDI) guidelines, the life-long goal Phe maintenance level range for patients of all ages is 2-6 mg/dL (120-360 mcmol/L).[11,12] There has been inconsistent published data regarding harm associated with Phe levels of 360-600 mcmol/L; however, there is no convincing evidence that these levels are without clinical effect.[11]. The recommended level is 2 to 6 mg/dL (120-360 mcmol/L) before conception and during pregnancy.[2,11,12]

Kuvan (sapropterin)
Sapropterin was studied in two pivotal trials in adults and one in children (ages 4-12 years).[5,6] All trials enrolled patients with PKU and had a primary endpoint of a 30% or greater reduction in Phe concentration.[5,6] All study patients continued on the PKU diet. Phe reductions greater than 30% ranged from 20% to 56% of patients in clinical trials.[5,6] The clinical significance of a 30% decrease in Phe is unknown. Another trial in 80 patients aged 4-12 years found that sapropterin allowed patients to increase dietary intake of protein.[7] Additional literature has shown safety and efficacy in patients less than 4 years of age.[9] An open label, single arm, multicenter trial was conducted with patients 1 month to 6 years of age (N=93). At screening, all patients in the study had a Phe level ≥ 360µmol/L. All were treated with 20 mg/kg with a concomitant Phe-restricted diet. Responders were defined as ≥30% decrease in blood Phe from baseline at week 4. Sixty-one percent or 57 patients were determined to be responders.[1]

An open label three-year extension trial of patients previously enrolled in sapropterin clinical trials was completed in 2011. Patients in this study were exposed to sapropterin at doses of 5mg/kg/day to 20 mg/kg/day for an average of 659 days[8]. The authors found that sapropterin was safe and well tolerated and maintained serum Phe within target range for most subjects[8]. Additional trials to establish the safety and efficacy of sapropterin as a long term treatment for PKU are ongoing.

The low protein diet in PKU has been shown to prevent serious complications of the disease like mental retardation. Sapropterin is not meant to replace and should be used in conjunction with the recommended PKU diet. Sapropterin response in clinical trials was not universal and sapropterin should be discontinued in patients that do not respond.[5,6] There is no genetic test or screening tool to predict response to sapropterin. Sapropterin is not indicated for any disease other than PKU.

Recommendations developed by specialized clinicians recommend all patients diagnosed with PKU receive a 1-2 month trial (25-50% of patients are responders), that efficacy and safety has been shown in patients < 4 years of age, that dosing be initiated between 5-20 mg/kg/day, that clinical response to therapy with sapropterin include reductions in blood Phe concentrations, increased dietary Phe tolerance, improved blood Phe stability, and improved neurocognitive and/or psychosocial functioning.[10,11]

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