**Phenylketonuria Prior Authorization Program Summary**

This program applies to FlexRx Open, FlexRx Closed, GenRx Open, GenRx Closed, Health Insurance Marketplace, Medicaid, FocusRx and KeyRx formularies.

This is a FlexRx Standard and GenRx Standard prior authorization program.

**FDA APPROVED INDICATIONS AND DOSAGE**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Dose</th>
</tr>
</thead>
</table>
| **Kuvan®** (sapropterin)  | Reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin-(BH4-) responsive phenylketonuria (PKU) | Initial dose: Patients 1 month to 6 years: 10 mg/kg once daily  
Patients 7 years and older: 10 to 20 mg/kg once daily  
Maintenance dose: dose may be adjusted to the range of 5 to 20 mg/kg taken once daily |
| **Palynziq™** (pegvalise-pqpz) subcutaneous injection | To reduce blood phenylalanine concentrations in adult patients with phenylketonuria who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management | 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>
<thead>
<tr>
<th>Titration</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 week</td>
<td>2.5 mg twice weekly</td>
<td>1 week</td>
</tr>
<tr>
<td>1 week</td>
<td>10 mg once weekly</td>
<td>1 week</td>
</tr>
<tr>
<td>1 week</td>
<td>10 mg twice weekly</td>
<td>1 week</td>
</tr>
<tr>
<td>1 week</td>
<td>10 mg four times per week</td>
<td>1 week</td>
</tr>
<tr>
<td>1 week</td>
<td>10 mg once daily</td>
<td>1 week</td>
</tr>
<tr>
<td>24 weeks</td>
<td>20 mg once daily</td>
<td>24 weeks</td>
</tr>
<tr>
<td>16 weeks</td>
<td>40 mg once daily</td>
<td>16 weeks</td>
</tr>
</tbody>
</table>

**CLINICAL RATIONALE**
Phenylketonuria (PKU), also known as phenylalanine hydroxylase (PAH) deficiency, is a rare autosomal recessive inborn error of phenylalanine (Phe) metabolism caused by variants in the gene encoding PAH. PAH deficiency leads to accumulation of Phe in the blood and brain.

Untreated, PKU is characterized by irreversible intellectual disability, microcephaly, motor deficits, eczematous rash, autism, seizures, developmental problems, aberrant behavior, and psychiatric symptoms. PKU was the first disorder to benefit from newborn screening in the 1960s and 1970s. Since the initiation of newborn screening, almost all cases of PAH deficiency are diagnosed following a positive newborn screening test. High blood Phe concentrations are strongly related to neurocognitive outcomes.

Over time, subtle intellectual and neuropsychiatric issues may manifest even with treatment. In addition, patients treated from the early weeks of life with initial good metabolic control, but who lose control later in childhood or adult life, may experience both reversible and irreversible neuropsychiatric consequences. Even severely intellectually disabled adults with late-diagnosed PAH deficiency show improvements in challenging behavior with lowering of blood Phe levels. Pregnancy presents a problem in women with PAH deficiency, as high levels of Phe are toxic to the brain of the developing fetus and along with other teratogenic effects, results in a defined maternal PKU syndrome.

Treatment is recommended to be taken as early as possible, preferably within the first week of life with a goal of having blood Phe in the treatment range within the first 2 weeks of life. All patients with untreated Phe blood concentration greater than 600 micromol/L should be treated. There is not clear consensus regarding clinical outcomes and treatment of Phe blood concentrations between 360 and 600 micromol/L. Guidelines recommend treatment for patients with untreated Phe concentrations between 360 and 600 micromol/L for the first 12 years of age, as good metabolic control during childhood appears essential to prevent cognitive function impairment in PKU. Treatment should be considered for women prior to conception with blood Phe > 360 micromol/L due to risks of maternal PKU. Most commonly reported blood Phe recommendations in the US are 120-360 micromol/L (2-6 mg/dL) for those < 12 years and 120-600 micromol/L (2-10 mg/dL) for those more than 12 years of age.

Treatment goals include neurocognitive and psychosocial functioning. Existing treatments aim at decreasing blood Phe concentrations, which remains the best surrogate measure and should be monitored regularly. Guidelines recommend patients less than 12 years of age should have blood Phe between 120 and 360 micromol/L. For patients 12 years of age and older, target Phe levels should be 120 to 600 micromol/L. Dietary therapy involving dietary Phe restriction and supplementation with reduced or Phe-free amino acid mixtures (medical foods, formulas) is the mainstay of therapy and effective in preventing severe mental retardation association with untreated classical PAH deficiency. Studies have demonstrated that it is unsafe to stop treatment during childhood and pre-adolescence. There is currently no strong evidence that it is safe to discontinue dietary treatment in adults, treatment for life is recommended, even though it is acknowledged that dietary management is associated with significant patient burden.

Sapropterin is a synthetic form of naturally occurring cofactor, tetrahydrobiopterin. Some patients with PAH deficiency who have some residual enzyme activity respond to administration of sapropterin with an increase in the metabolism of Phe to tyrosine. Approximately 25-50% of patients with PAH deficiency are sapropterin responsive. A significant decline in blood Phe is expected in responders with the assumption that diet remains stable with sapropterin therapy. Clinical judgment is required to determine what constitutes as a significant or beneficial decline in an individual patient but 30% is often cited as evidence of effective Phe reduction. However, patients on the lower end of blood Phe level
(180 micromol/L or lower) rarely show a significant decline in blood Phe levels. Clinical trials for sapropterin identified responders as ≥ 30% decrease in blood Phe from baseline.

Pegvaliase-pqpz is a phenylalanine-metabolizing enzyme indicated to reduce blood Phe in adult patients with PKU who have uncontrolled blood Phe greater than 600 micromol/L on existing management. Existing management options include prior or current restriction of dietary phenylalanine and protein intake, and/or prior treatment with sapropterin dihydrochloride. Patients previously treated with sapropterin dihydrochloride were required to discontinue use at least 14 days prior to the first dose. Patients should discontinue pegvaliase-pqpz if they did not achieve at least a 20% reduction in blood phenylalanine concentration from pre-treatment baseline or have 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.

REFERENCES
Phenylketonuria Prior Authorization

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 AGENTS
Kuvan® (sapropterin)
Palynziq™ (pegvaliase-pqpz)

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
INITIAL EVALUATION
The target agent will be approved when ALL of the following are met:
1. The patient has a diagnosis of phenylketonuria (PKU)
   AND
2. The patient is currently on a phenylalanine (Phe) restricted diet and will continue while being treated with the requested agent
   AND
3. The prescriber has submitted a baseline blood Phe level
   AND
4. ONE of the following:
   a. The requested agent is Kuvan AND ONE of the following:
      i. The patient is less than 12 years of age AND has baseline blood Phe level >360 micromol/L (6 mg/dL) OR
      ii. The patient is 12 years of age or over AND has baseline blood Phe level greater than 600 micromol/L (10 mg/dL) OR
      iii. The patient is planning on becoming pregnant OR is currently pregnant AND has a baseline Phe level >360 micromol/L (6 mg/dL)
   OR
   b. If the requested agent is Palynziq, then BOTH of the following:
      i. The patient is an adult AND
      ii. The patient has a baseline blood Phe level greater than 600 micromol/L (10 mg/dL)
   AND
5. 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
6. ONE of the following:
   a. The patient is NOT currently being treated with another targeted agent included in this program OR
   b. The patient is currently being treated with another targeted agent included in this program AND will be discontinued prior to initiating the requested agent
   AND
7. The patient does NOT have any FDA labeled contraindication(s) to the requested agent
   AND
8. 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**: 9 months

**RENEWAL EVALUATION**

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

1. The patient has been previously approved for the requested agent through the Prime Therapeutics PA process
   **AND**
2. The patient has received clinical benefit with the requested agent AND ONE of the following:
   a. If the requested agent is Kuvan, then ONE of the following:
      i. The patient's blood Phe levels are being maintained within the acceptable range [< 12 years of age and for females currently pregnant or planning on becoming pregnant: 120-360 mc mol/L (2-6 mg/dL); ≥12 years of age: 120-600 micromol/L (2-10 mg/dL)]
      **OR**
      ii. The patient has had a ≥30% decrease in blood Phe level from baseline
   **OR**
   b. If the requested agent is Palynziq, then ONE of the following:
      i. The patient's blood Phe level is ≤600 micromol/L (10 mg/dL) **OR**
      ii. The patient has had a ≥20% decrease in blood Phe level from baseline
      **OR**
      iii. The patient has NOT received more than 16 weeks of therapy at the maximum recommended dose in approved labeling (40 mg daily) AND the prescriber will evaluate for a dose escalation to induce clinical response
   **AND**
3. The patient is currently on a phenylalanine (Phe) restricted diet and will continue while being treated with the requested agent
   **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. ONE of the following:
   a. The patient is NOT currently being treated with another targeted agent included in this program **OR**
   b. The patient is currently being treated with another targeted agent included in this program AND will discontinue prior to continuing the requested agent
   **AND**
6. The patient does NOT have any FDA labeled contraindication(s) to the requested agent
   **AND**
7. The dose is within the FDA-labeling

**Length of Approval**: 12 months