Phenylketonuria Agents

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO148

Description

Pegvaliase (Palynziq) is a PEGylated phenylalanine-metabolizing enzyme that works to reduce blood phenylalanine concentrations by converting phenylalanine to ammonia and transcinnamic acid.

Sapropterin dihydrochloride (Kuvan) is a synthetic form of the cofactor BH4 (tetrahydrobiopterin) for the enzyme phenylalanine hydroxylase (PAH). PAH hydroxylates phenylalanine to form tyrosine. BH4 activates residual PAH enzyme, improving normal phenylalanine metabolism and decreasing phenylalanine levels.

Length of Authorization

- Initial:
  - Pegvaliase (Palynziq): Six months
  - Sapropterin dihydrochloride (Kuvan): Two months
- Renewal:
  - Pegvaliase (Palynziq): 12 months
  - Sapropterin dihydrochloride (Kuvan): 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
pegvaliase (Palynziq)	2.5 mg/0.5 mL	Phenylketonuria (PKU)	8 syringes/30 days
	10 mg/0.5 mL		30 syringes/30 days
	20 mg/1 mL		90 syringes/30 days
sapropterin dihydrochloride (generic Kuvan)	100 mg tablets		20 mg/kg/day
	100 mg powder for oral solution		
	500 mg powder for oral solution		
sapropterin dihydrochloride (Kuvan)	100 mg tablets		20 mg/kg/day
	100 mg powder for oral solution		

	500 mg powder for oral solution		
sapropterin dihydrochloride (Javygtor)	100 mg tablets		20 mg/kg/day
	100 mg powder for oral solution		
	500 mg powder for oral solution		

Initial Evaluation

I. **Pegvaliase (Palynziq), sapropterin dihydrochloride (Kuvan), and sapropterin dihydrochloride (Javygtor)** may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a metabolic diseases specialist or a provider who specializes in the treatment of phenylketonuria and other metabolic disorders; **AND**
   B. Documentation of current blood phenylalanine concentration is submitted; **AND**
   C. Documentation noting member compliance with a phenylalanine restricted diet; **AND**
   D. Member is going to continue to restrict phenylalanine from their diet; **AND**
   E. A diagnosis of **phenylketonuria (PKU)** when the following are met:
      1. Request is for **generic sapropterin sapropterin dihydrochloride**; **AND**
         i. Member has tetrahydrobiopterin- (BH4-) responsive PKU; **AND**
         ii. Member has uncontrolled blood phenylalanine concentrations greater than 360 micromol/L on existing management [e.g., phenylalanine restricted diet]; **AND**
         iii. Not used in combination with pegvaliase (Palynziq); **OR**
      2. Request is for **pegvaliase (Palynziq)**; **AND**
         i. Member is 18 years of age or older; **AND**
         ii. Member has uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management [e.g., phenylalanine restricted diet, Kuvan (sapropterin)]; **AND**
         iii. Not used in combination with sapropterin dihydrochloride (Kuvan); **OR**
      3. Request is for **dihydrochloride (Kuvan) or sapropterin dihydrochloride (Javygtor)**; **AND**
         i. Member has tetrahydrobiopterin- (BH4-) responsive PKU; **AND**

ii. Member has uncontrolled blood phenylalanine concentrations greater than 360 micromol/L on existing management [e.g., phenylalanine restricted diet]; **AND**
iii. Treatment with generic sapropterin dihydrochloride (generic for Kuvan) has been ineffective, contraindicated, or not tolerated; **AND**
iv. Not used in combination with pegvaliase (Palynziq).

II. Pegvaliase (Palynziq) and sapropterin dihydrochloride (Kuvan) is considered investigational when used for all other conditions, including but not limited to:
   A. Liver Cirrhosis and Portal Hypertension
   B. Autism spectrum disorder
   C. Gastroparesis
   D. Schizophrenia

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Medication is prescribed by, or in consultation with, a metabolic diseases specialist or a provider who specializes in the treatment of phenylketonuria and other metabolic disorders; **AND**
IV. Documentation noting member compliance with a phenylalanine restricted diet; **AND**
V. Documentation of current blood phenylalanine concentration is submitted; **AND**
VI. Attestation of member compliance to therapy with pegvaliase (Palynziq) or sapropterin dihydrochloride (Kuvan); **AND**
VII. Member had a response to pegvaliase (Palynziq) therapy defined as:
   - At least a 20% reduction in blood phenylalanine levels from baseline; **OR**
   - Blood phenylalanine concentration less than or equal to 600 micromol/L; **OR**
VIII. Member had a response to sapropterin dihydrochloride (Kuvan) therapy defined as:
   - At least a 30% reduction in in blood phenylalanine levels from baseline

Supporting Evidence

I. Phenylketonuria (PKU) is an inherited disorder that increases the levels of a substance called phenylalanine in the blood. If PKU is not treated, phenylalanine can build up to harmful levels in the body causing intellectual disability and other serious health problems. Seizures, delayed development, behavioral problems, and psychiatric disorders are also common. Considering all the aspects of this disease state and that it is crucial to identify if a member is responding to therapy, the medication needs to be prescribed by, or in consultation with, a metabolic diseases specialist or a provider who specializes in the treatment of phenylketonuria and other metabolic disorders.

II. For sapropterin dihydrochloride (Kuvan) the response to therapy is determined by change in blood phenylalanine following treatment. If blood phenylalanine does not decrease from baseline at 10 mg/kg per day, the dose may be increased to 20 mg/kg per day. Patients whose blood phenylalanine does not decrease after 1 month of treatment at 20 mg/kg per day are non-responders and treatment should be discontinued.

III. For pegvaliase (Palynziq) the response to therapy is determined by change in blood phenylalanine following 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 less than or equal to 600 micromol/L) after 16 weeks of continuous treatment with the dosage of 40 mg once daily, can consider increasing to a maximum dose of 60 mg once daily. Pegvaliase (Palynziq) should be discontinued in patients who have not achieved an adequate response after 16 weeks of continuous treatment with the maximum dosage of 60 mg once daily.

IV. It is crucial for treatment and prevention of disease progression to obtain the blood levels of phenylalanine prior to treatment start.

V. According to the American College of Medical Genetics and Genomics (ACMG) Practice Guidelines, dietary therapy, with restriction of dietary phenylalanine intake, remains the mainstay of therapy for PAH deficiency. The goal of the diet is to provide enough natural protein for the patient to be healthy and grow normally with sufficient restriction to keep blood phenylalanine in the treatment range. PKU medication is not a replacement for diet.

VI. Pegvaliase (Palynziq) is indicated to reduce blood phenylalanine concentrations in adult patients with PKU who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management [e.g., phenylalanine restricted diet, Kuvan (sapropterin)].

VII. The safety and efficacy of pegvaliase (Palynziq) in pediatric patients has not been assessed in clinical trials and therefore there is no robust evidence to support the use. However, pegvaliase (Palynziq) has been approved in the European Union for patients age 16 years or older with a dose regimen that mirrors adult dosing. Additionally, three open label phase 2 studies evaluating use of Palynziq in patients age 16 years or older have been completed in the U.S. (NCT01560286, NCT00925054, NCT00924703) which show some signals of efficacy. However,

studies have a small sample size, low enrollment of patients age <18 years, and possible safety concerns, thus true safety and efficacy of Palynziq in the subset of patients age 16 to 18 years remains unknown.

VIII. There is no robust clinical trial data to show an increase benefit and the safety profile of concomitant use of pegvaliase (Palynziq) and sapropterin dihydrochloride (Kuvan).

IX. Sapropterin dihydrochloride (Kuvan) is indicated to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4-) responsive PKU. Kuvan is to be used in conjunction with a Phe-restricted diet.

Investigational or Not Medically Necessary Uses

I. Pegvaliase (Palynziq);
   A. There is limited or no published clinical trial data to support the use of pegvaliase (Palynziq) in conditions other than PKU.

II. Sapropterin dihydrochloride (Kuvan);
   A. Liver Cirrhosis and Portal Hypertension
      i. A randomized, blinded, and placebo controlled trial was conducted to assess the effects of sapropterin dihydrochloride (Kuvan) on hepatic and systemic hemodynamics in patients with liver cirrhosis and portal hypertension. The trial data showed that sapropterin dihydrochloride (Kuvan), did not reduce portal pressure in patients with cirrhosis.
   B. Autism spectrum disorder (ASD)
      i. A prospective 16-week open-label outpatient treatment trial of sapropterin dihydrochloride (Kuvan) for core and associated ASD symptoms in 2–6-year-old children with confirmed language and/or social delays extended the understanding of the effect of BH_4 treatment on the cognitive and behavioral symptoms of individuals with ASD
      ii. The results of a double-blind placebo-controlled crossover study, designed to examine the tetrahydrobiopterin pathway genes in autism, indicated a possible effect of BH4 treatment in children with autistic disorder, but the study does not have enough power and it wasn't designed to show efficacy and safety of the use of sapropterin dihydrochloride (Kuvan) in the treatment of autism spectrum disorder. There is no robust safety and efficacy data to support the use of sapropterin dihydrochloride (Kuvan) in patients with autism spectrum disorder.
   C. Gastroparesis
      i. One small open label trial consisting of low quality evidence. Further evaluation is needed to support the use of sapropterin dihydrochloride (Kuvan) in this setting.
   D. Schizophrenia

i. One small open label trial consisting of low quality evidence is available with ongoing trials recruiting as of 2019. Further evaluation is need to support use of sapropterin dihydrochloride (Kuvan) in this setting.

References

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14. ClinicalTrials.gov. Kuvan in People With Schizophrenia and Schizoaffective Disorder. NCT01706965.
15. European Commission approves Palynziq® (Pegvaliase injection) for treatment of phenylketonuria (PKU) in patients aged 16 years or older. BioMarin Investors. Available at: https://investors.biomarin.com/2019-05-06-European-Commission-Approves-Palynziq-R-pegvaliase-injection-for-Treatment-of-Phenylketonuria-PKU-in-Patients-Aged-16-Years-or-Older
16. ClinicalTrials.gov. A Study to Evaluate Subcutaneously Administered rAvPAL-PEG in Patients With Phenylketonuria for 24 Weeks. NCT01560286.
17. ClinicalTrials.gov. Dose-Finding Study to Evaluate the Safety, Efficacy, & Tolerability of Multiple Doses of rAvPAL-PEG in Subjects With PKU. NCT00925054.
18. ClinicalTrials.gov. Long-Term Extension of Previous rAvPAL-PEG Protocols in Subjects With PKU (PAL-003). NCT00924703.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added branded sapropterin dihydrochloride (Javygtor) to policy	11/2022
Addition of generic sapropterin dihydrochloride (generic Kuvan) into policy, requiring trial of generic prior to brand. Updates to QL, allowing for 60 mg max dose. Formatting updates and updates to supporting evidence.	10/2021
• Updated criteria to policy format and combined separate polices into one • Ensured sapropterin dihydrochloride (Kuvan) is not used in combination with pegvaliase (Palynziq) • Requirement of member requesting sapropterin dihydrochloride (Kuvan) to have tetrahydrobiopterin- (BH4-) responsive PKU • Added criteria to require documentation of current blood phenylalanine concentration and of current compliance with a phenylalanine restricted diet • Adjusted requirement of phenylalanine levels in use of sapropterin dihydrochloride (Kuvan) to be greater than 360 micromol/L for all ages • Updated renewal duration with Kuvan to 1 year to align with Palynziq	12/2019
pegvaliase (Palynziq) policy effective	08/2018
sapropterin dihydrochloride (Kuvan) policy effective	02/2009