

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

sapropterin dihydrochloride (Javygtor)		500 mg powder for oral solution	
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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 dihydrochloride**; **AND**
 - i. Member has uncontrolled blood phenylalanine concentrations greater than 360 micromol/L on existing management [e.g., phenylalanine restricted diet]; **AND**
 - ii. 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. Attestation noting member compliance with a phenylalanine restricted diet; **AND**
- IV. Documentation of current blood phenylalanine concentration is submitted; **AND**
- V. Attestation of member compliance to therapy with pegvaliase (Palynziq) or sapropterin dihydrochloride (Kuvan; Javygtor); **AND**
- VI. Member had a response to pegvaliase (Palynziq) therapy defined as:
 - A. At least a 20% reduction in blood phenylalanine levels from baseline; **OR**
 - B. Blood phenylalanine concentration less than or equal to 600 micromol/L; **OR**
- VII. Member had a response to generic sapropterin dihydrochloride or sapropterin dihydrochloride (Kuvan; Javygtor) therapy defined as:
 - A. At least a 30% reduction in in blood phenylalanine levels from baseline; **OR**
 - B. Clinical response (e.g., cognitive and/or behavioral improvements)

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. It is crucial for treatment and prevention of disease progression to obtain the blood levels of phenylalanine (PHE) prior to treatment start.
- III. 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.

- IV. Pegvaliase (Palynziq) is FDA approved 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)].
- V. 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 aged 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 aged 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 less than 18 years old, and possible safety concerns, thus true safety and efficacy of Palynziq in the subset of patients aged 16 to 18 years remains unknown.
- VI. 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).
- VII. ACMG guidelines note that approximately 25–50% of the patients with PAH deficiency are sapropterin-responsive. Patients with mild PAH deficiency are most likely to respond because some stable protein is required for sapropterin to function; nonetheless, responsive patients are identified even among those with complete PAH deficiency. Genotype may be predictive of sapropterin response, but genotype-phenotype correlations thus far are imperfect. Therefore, every PAH-deficient patient should be offered a trial of sapropterin therapy to assess responsiveness. Clinical judgment is required to determine what constitutes a significant or beneficial decline in an individual patient, but 30% is often cited in the literature as evidence of effective PHE reduction. Most sapropterin responsive patients have a rapid decline in blood PHE level, but occasionally a delay of 2–4 weeks is seen. Patients with a baseline PHE level at the lower end of the treatment range (180 μ mol/l or lower) rarely show a significant decline in blood PHE level, even if they are sapropterin-responsive. An improvement in neuropsychiatric symptoms or increase in PHE tolerance without a decrease in blood PHE in any patient constitutes sufficient justification to continue therapy. The blood phenylalanine concentration associated with optimal neurodevelopmental outcome is uncertain.
- VIII. 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. However, an improvement in neuropsychiatric symptoms constitutes sufficient justification to continue therapy.

- IX. 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. As recommended in the package insert, 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.

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 BH₄ 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 needed to support use of sapropterin dihydrochloride (Kuvan) in this setting.

References

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2. Kuvan [package insert]. Novato, CA: BioMarin Pharmaceutical Inc; March 2020.
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4. Phenylketonuria: Screening and Management. NIH Consensus Statement Online 2000 October 16-18; 17(3): 1-27 Accessed 01/19/2009.
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13. ClinicalTrials.gov. Impact of KUVAN® on Gastric Relaxation in Women With Diabetic Gastroparesis. NCT01135186.
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.

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
For sapropterin: Removal of BH4 responsiveness at initial as this is evaluated via medication trial. Updated renewal criteria to allow continuation in those with neurocognitive improvement as per ACMG guidelines. Removed requirement of specialist prescribing upon renewal, this update is applicable to all agents.	03/2023
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
<ul style="list-style-type: none"> Updated criteria to policy format and combined separate policies 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