# PRIOR AUTHORIZATION POLICY

**POLICY:** Phenylketonuria – Kuvan® (sapropterin dihydrochloride tablets and powder for oral solution – BioMarin Pharmaceuticals) Prior Authorization Policy

**REVIEW DATE:** 06/17/2020

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## OVERVIEW

Kuvan is indicated to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin-(BH4) responsive phenylketonuria (PKU).[1] The medication should be used with a Phe-restricted diet. Kuvan works by increasing phenylalanine hydroxylase (PAH). It is a synthetic preparation of naturally occurring BH4, which is a cofactor for the enzyme PAH. PAH hydroxylates Phe in an oxidative reaction to form tyrosine. In patients with PKU, PAH activity is deficient or absent. Treatment with BH4 can activate residual PAH enzyme, improve the normal oxidative metabolism of Phe, and decrease Phe levels in some patients.

PKU is the most prevalent disorder due to an inborn error in amino acid metabolism.[3] It is caused by mutations in the PAH gene.[3] The annual incidence is about 1:15,000 births in the US. Genotypes of the disease range from a mild increase in blood Phe concentrations to a severe classic phenotype with very pronounced increases in HPA, which if not treated, can result in profound and irreversible mental disability.[3] Dietary restrictions in Phe are a mainstay in PKU management. Patients with PKU have to intake Phe-free formula and avoid foods that are protein-rich (e.g., meats, fish, eggs, standard bread, most cheeses, nuts and seeds). Other foods and beverages that contain aspartame, flour, soy, beer, or cream should be avoided. Low-protein foods that are natural may be consumed in restricted amounts, such as potatoes, some vegetables, and most cereals. During infancy, adherence to dietary restrictions is more manageable but as children grow older and become adults the dietary limitations can become burdensome.

### Dose Titration

In patients with PKU who are responsive to treatment, blood Phe levels decrease within 24 hours after administration, although maximal effect on Phe levels may take up to 1 month. Blood Phe levels should be checked after 1 week of treatment and periodically for 1 month. If blood Phe does not decrease from baseline at the 10 mg/kg/day dose, the dose may be increased to 20 mg/kg/day. Patients whose blood Phe does not decrease after 1 month of treatment at 20 mg/kg/day are non-responders and treatment with Kuvan should be discontinued. Once responsiveness has been determined, the dose may be adjusted within the range of 5 to 20 mg/kg/day.

### Guidelines/Recommendations

According to the European guidelines for phenylketonuria (2017), there is consensus in the literature that patients with blood phenylalanine concentration > 600 µmol/L should be treated.[8] There is also consensus that patients with blood Phe concentration < 360 µmol/L can remain untreated, but should be monitored. Patients with blood Phe concentration between 360 to 600 µmol/L should be treated until 12 years of age. Treatment for life is recommended for any patient with PKU; however, it is also noted that patients ≥ 12 years of age with blood Phe concentration < 600 µmol/L do not require treatment. All adults with PKU should have lifelong systematic follow-ups in specialized metabolic centers, due to specific risks which may occur during adulthood. With regards to target Phe levels, in treated PKU patients up to 12 years of age, the target Phe levels should be 120 to 360 µmol/L; in treated PKU patients ≥ 12 years of age, the target Phe levels should be 120 to 600 µmol/L.

The American College of Medical Genetics and Genomics (ACMG) published practice guidelines (2014) for the diagnosis and management of PAH deficiency.[9] The guidelines recommend initiating treatment as early as possible, preferably within the first week of life with a goal of having blood Phe levels in the treatment range within the first 2 weeks. Dietary restriction of Phe intake is the mainstay of therapy for PKU. Blood Phe levels in all patients should be maintained in the range of 120 to 360 µmol/L. Newly diagnosed infants should be monitored at least weekly for their levels at least until 1 year of age. For children 1 through 12 years of age, biweekly to monthly monitoring of levels is adequate and for adolescents and adults who are stable and well-controlled, monthly testing is usually adequate. The guidelines state that approximately 25% to 50% of patients with PAH deficiency are responsive to Kuvan. A significant decline in blood Phe level is expected in responders once treatment is initiated (with Phe-restricted diet); however, patients in the lower end of the treatment range (≤ 180 µmol/L) rarely show a decrease in blood Phe level even if they are responsive to Kuvan. In these patients, responsiveness is determined by adding Phe to the diet in a stepwise method. An improvement in neuropsychiatric symptoms or increase in Phe tolerance without a decrease in blood Phe levels is sufficient reasoning to continue therapy. According to the guidelines, there is strong evidence to support life-long treatment and maintenance of metabolic control in patients with PAH deficiency.

## POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Kuvan tablets and powder for oral solution. Because of the specialized skills required for evaluation and diagnosis of patients treated with Kuvan as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Kuvan to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 1 year in duration unless otherwise noted below.

**Automation:** None.

## RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Kuvan tablets or Kuvan powder for oral solution is recommended in those who meet the following criteria:

### FDA-Approved Indications

1. **Phenylketonuria.** Approve for the duration noted if the patient meets the following criteria (A or B):
   - **A)** Initial Therapy: Approve for 12 weeks if the patient meets the following criteria (i and ii):
     - **i.** Kuvan is prescribed in conjunction with a phenylalanine (Phe)-restricted diet; AND
     - **ii.** The medication is prescribed by or in consultation with a metabolic disease specialist (or specialist who focuses in the treatment of metabolic diseases).
   - **B)** Patients Continuing Therapy: Approve for 1 year if the patient meets the following criteria (i and ii):

     Note: Patients who have received < 12 weeks of therapy or those who are restarting therapy with Kuvan should be considered under criterion 1A (Phenylketonuria – Initial Therapy).
     - **i.** The patient meets one of the following (a, b, or c):
       - **a)** The patient has had a clinical response (e.g., cognitive and/or behavioral improvements) as determined by the prescriber; OR
       - **b)** The patient has achieved a ≥ 20% reduction in blood phenylalanine concentration from pre-treatment baseline (i.e., blood phenylalanine concentration before starting Kuvan therapy); OR

**c)** Treatment with Kuvan has resulted in an increase in dietary phenylalanine tolerance, according to the prescriber; AND

**ii.** The patient is not receiving concomitant Palynziq.

## CONDITIONS NOT RECOMMENDED FOR APPROVAL

Kuvan has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

**1.** Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

## REFERENCES

1. Kuvan™ tablets and powder for oral solution [prescribing information]. Novato, CA: BioMarin Pharmaceuticals; March 2020.
2. Levy H, Burton B, Cederbaum S, Scriver C. Recommendations for evaluation of responsiveness to tetrahydrobiopterin (BH4) in phenylketonuria and its use in treatment. *Mol Genet Metab*. 2007;92:287-291.
3. Blau N, van Spronsen FJ, Levy HL. Phenylketonuria. *Lancet*. 2010;376:1417-1427.
4. Feillet F, van Spronsen FJ, MacDonald A, et al. Challenges and pitfalls in the management of phenylketonuria. *Pediatrics*. 2010;126(2):333-341.
5. Levy HL, Milanowski A, Chakrapani A, et al for the Sapropterin Research Group. Efficacy of sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH4) for reduction of phenylalanine concentration in patients with phenylketonuria: a phase III randomized placebo-controlled study. *Lancet*. 2007;370:504-510.
6. Burton BK, Bausell H, Katz R, et al. Sapropterin therapy increases stability of blood phenylalanine levels in patients with BH4-responsive phenylketonuria (PKU). *Mol Genet Metab*. 2010;101(2-3):110-114.
7. Burton BK, Nowacka M, Hennermann JB, et al. Safety of extended treatment with sapropterin dihydrochloride in patients with phenylketonuria: results of a phase 3b study. *Mol Genet Metab*. 2011;103(4):315-322.
8. van Wegberg AMJ, MacDonald A, Ahring A, et al. The complete European guidelines on phenylketonuria: diagnosis and treatment. *Orphanet J Rare Dis*. 2017;12:162.
9. Vockley J, Andersson HC, Antshel KM, et al. Phenylalanine hydroxylase deficiency: diagnosis and management guideline. Available at: https://www.acmg.net/docs/Phenylalanine_Hydrosylase_Deficiency_Practice_Guideline_AOP_Jan_2013.pdf. Accessed on June 5, 2020.