Prior Authorization
Phenylketonuria – Kuvan® (sapropterin dihydrochloride tablets and powder for oral solution, generic)

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Product Identifier(s)

Effective through 12/31/2022: 33900
Effective 1/1/2023: 109036

INSTRUCTIONS FOR USE
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National Formulary Medical Necessity

Cigna covers sapropterin dihydrochloride (Kuvan®) as medically necessary when the following criteria are met for FDA Indications or Other Uses with Supportive Evidence:

Prior Authorization is recommended for prescription benefit coverage of sapropterin (Kuvan, generic). Because of the specialized skills required for evaluation and diagnosis of individuals treated with sapropterin as well as the monitoring required for adverse events and long-term efficacy, initial approval requires sapropterin to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

FDA Indication(s)

1. **Phenylketonuria.** Approve for the duration noted if the individual meets the following criteria (A or B):
   - **A)** Initial Therapy. Approve for 12 weeks if the individual meets the following criteria (i and ii):
     - **i.** Sapropterin is prescribed in conjunction with a phenylalanine-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) Individuals is Currently Receiving Sapropterin (Kuvan, generic). Approve for 1 year if the individual meets the following criteria (i and ii):
Note: A individual who has received < 12 weeks of therapy or who is restarting therapy with sapropterin should be considered under Initial Therapy.

i. Individual meets one of the following (a, b, or c):

a) Individual has had a clinical response (e.g., cognitive and/or behavioral improvements) as determined by the prescriber; OR

b) Individual has achieved a ≥ 20% reduction in blood phenylalanine concentration from pre-treatment baseline (i.e., blood phenylalanine concentration before starting sapropterin therapy); OR

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

ii. Individual is not receiving concomitant Palynziq (pegvaliase-pqpz subcutaneous injection) at a stable maintenance dose.
Note: Concomitant use with Palynziq is permitted during Palynziq dose titration.

Conditions Not Covered

Sapropterin dihydrochloride (Kuvan®) is considered experimental, investigational or unproven for ANY other use.

Background

Overview
Sapropterin (Kuvan, generic), a synthetic form of the cofactor for the enzyme phenylalanine hydroxylase, is indicated to reduce blood phenylalanine levels in patients with hyperphenylalaninemia due to tetrahydrobiopterin-responsive **phenylketonuria** (PKU).[1] The medication should be used with a phenylalanine-restricted diet. Of note, some patients do not show a biochemical response to sapropterin. Per the prescribing information, biochemical response cannot generally be predetermined by laboratory testing and should be determined through a therapeutic trial (evaluation) of sapropterin response.

Dose Titration
The initial starting dose of sapropterin is either 10 mg/kg per day or 20 mg/kg per day. If a 10 mg/kg per day starting dose is used, the dose should be increased to 20 mg/kg if the patient's blood phenylalanine does not decrease after 1 month of treatment. If blood phenylalanine does not decrease after 1 month of treatment on 20 mg/kg per day, sapropterin should be discontinued.

Guidelines/Recommendations
According to the European guidelines for PKU (2017), there is consensus in the literature that patients with blood phenylalanine concentration > 600 micromol/L should be treated.[8] There is also consensus that patients with blood phenylalanine concentration < 360 micromol/L can remain untreated, but should be monitored. Patients with blood phenylalanine concentration between 360 to 600 micromol/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 phenylalanine concentration < 600 micromol/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 phenylalanine levels, in treated PKU patients up to 12 years of age, the target levels should be 120 to 360 micromol/L; in treated PKU patients ≥ 12 years of age, the target levels should be 120 to 600 micromol/L.

The American College of Medical Genetics and Genomics (ACMG) published practice guidelines (2014) for the diagnosis and management of phenylalanine hydroxylase (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 phenylalanine levels in the treatment range within the first 2 weeks. Dietary restriction of phenylalanine intake is

the mainstay of therapy for PKU. Blood phenylalanine levels in all patients should be maintained in the range of 120 to 360 micromol/L. The guidelines state that approximately 25% to 50% of patients with PAH deficiency are responsive to sapropterin. A significant decline in blood phenylalanine level is expected in responders once treatment is initiated (with phenylalanine-restricted diet); however, patients in the lower end of the treatment range (≤ 180 micromol/L) rarely show a decrease in blood phenylalanine level even if they are responsive to sapropterin. In these patients, responsiveness is determined by adding phenylalanine to the diet in a stepwise method. An improvement in neuropsychiatric symptoms or increase in phenylalanine tolerance without a decrease in blood phenylalanine 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.

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 July 28, 2022.

Revision History

Type of Revision	Summary of Changes	Approval Date
Annual Revision	No criteria changes.	08/10/2022