BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

**PHARMACY COVERAGE GUIDELINE**

# KUVAN® (sapropterin dihydrochloride) oral
# Sapropterin Dihydrochloride oral

**This Pharmacy Coverage Guideline (PCG):**
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

**Scope**
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

**Instructions & Guidance**
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require precertification is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

## Criteria:

- **Criteria for initial therapy:** Kuvan (sapropterin dihydrochloride) or sapropterin dihydrochloride is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a specialist with knowledge and expertise in metabolic diseases or genetic diseases

  2. Individual is 1 month of age or older

  3. A confirmed diagnosis of hyperphenylalaninemia (HPA) due to tetrahydrobiopterin (BH4) responsive phenylketonuria (PKU)

  4. Individual is on a phenylalanine (PHE)-restricted diet

5. **ALL** of the following baseline tests have been completed before initiation of treatment:
    a. Phenylalanine (PHE) level is above the recommended level for the individual's age or condition (baseline value must be submitted with the request)

6. Request for **brand** Kuvan: Individual has failure, contraindication or intolerance to **generic sapropterin dihydrochloride**

7. Will not be used concurrently with Palynziq (pegvaliase-pqpz)

8. There are no significant interacting drugs

**Initial approval duration:** 3 months

- **Criteria for continuation of coverage (renewal request):** Kuvan (sapropterin dihydrochloride) or sapropterin dihydrochloride is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met (**samples are not considered for continuation of therapy**):

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a specialist with knowledge and expertise in metabolic diseases or genetic diseases

2. PHE-restricted diet was not changed in any way during the initial trial of therapy with Kuvan in order to determine responsiveness

3. Individual's condition responded while on therapy with response defined as: Baseline PHE level and the most recent PHE level show at least a 30% decrease in PHE while on Kuvan (levels must be submitted when requesting continued treatment

4. Individual has been adherent with the medication

5. Request for continuation of **brand** Kuvan: Individual has failure, contraindication or intolerance to **generic sapropterin dihydrochloride**

6. Will not be used concurrently with Palynziq (pegvaliase-pqpz)

7. There are no significant interacting drugs

**Renewal duration**: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

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# Sapropterin Dihydrochloride oral

## Description:

Sapropterin dihydrochloride (brand Kuvan or generic) is an orally administered phenylalanine (PHE) hydroxylase activator approved to reduce blood PHE levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin (BH4)-responsive phenylketonuria (PKU). Left untreated the condition can lead to profound neurocognitive and developmental defects. Neurologic damage can include severe mental retardation, microcephaly, delayed speech, seizures, and behavioral abnormalities. Conversely, prolonged low levels of blood PHE have been associated with catabolism and protein breakdown.

The underlying defect seen is a deficiency or a decrease in activity of the hepatic enzyme phenylalanine hydroxylase (PAH). PAH deficiency is an autosomal-recessive disorder. The gene is located on chromosome 12. More than 500 different mutations in the PAH gene have been described.

Sapropterin dihydrochloride is a biologically active synthetic form of naturally occurring BH4. It reduces blood PHE levels in patients with HPA by improving the normal metabolism of PHE. BH4 is a cofactor for the enzyme phenylalanine hydroxylase (PAH) that hydroxylates PHE through an oxidative reaction to form tyrosine (TYR). PAH activity is absent or deficient among patients with PKU. While these individuals are not deficient in endogenous BH4, some patients with PAH deficiency, who have some residual enzyme activity respond to administration of sapropterin dihydrochloride with an increase in the metabolism of PHE to TYR.

The mechanism by which residual PAH activity is enhanced is unclear, but BH4 may act as a pharmacologic chaperone leading to improved folding and increased stability of the mutant protein. In clinical trials, approximately 20–75% of the patients with PAH deficiency are BH4-responsive. Patients whose blood PHE does not decrease after 1 month of treatment at 20 mg/kg per day are considered non-responders and treatment with sapropterin dihydrochloride should be discontinued in these patients. Current literature cites a 30% reduction in PHE levels as evidence for responsiveness to sapropterin dihydrochloride.

Sapropterin dihydrochloride must be used in conjunction with a PHE restricted diet. Active management of dietary PHE intake is the mainstay of therapy and requires restriction of dietary PHE intake necessitating a decrease in the intake of natural protein and replacing it with a protein (amino acid mixture) source devoid of PHE. A provider experienced in metabolic disorders and a nutritionist team-based approach should manage this therapy. Dietary manipulation will be required to maintain appropriate blood PHE levels with frequent dietary modification to respond to growth, life stages, concurrent illness, and comorbidities.

The American College of Medical Genetics and Genomics 2014 practice guideline suggests blood PHE levels should be maintained in the range of 120–360 µmol/L for all patients, although there is no evidence to suggest normalization of PHE levels is required and lower levels of 60-120 µmol/L should not be viewed as too low. It should be noted that measurement of PHE levels in blood varies and is dependent on the analytical method used; requiring consistency in testing methodology in order to interpret the resultant values.

## Resources:

Kuvan (sapropterin) product information, revised by BioMarin Pharmaceutical, Inc. 02-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed December 24, 2021.

Sapropterin product information, revised by Dr. Reddys Laboratories, Inc. 09-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed December 24, 2021.

Bodamer OA. Overview of phenylketonuria. In: UpToDate, Hahn S, TePas E (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Topic last updated July 17, 2020. Accessed December 24, 2021.