



PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 3/19/15
LAST REVIEW DATE: 3/15/18
LAST CRITERIA REVISION DATE: 3/15/18
ARCHIVE DATE:

KUVAN® (sapropterin dihydrochloride) oral pack and soluble tablet

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

KUVAN® (sapropterin dihydrochloride) oral pack and soluble tablet (cont.)

Description:

- Kuvan (sapropterin dihydrochloride) 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
- Kuvan (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 Kuvan (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 Kuvan (sapropterin dihydrochloride) should be discontinued in these patients
- Current literature cites a 30% reduction in PHE levels as evidence for responsiveness to Kuvan (sapropterin dihydrochloride)
- Kuvan (sapropterin dihydrochloride) must be used in conjunction with a PHE restricted diet

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- 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 $\mu\text{mol/L}$ for all patients, although there is no evidence to suggest normalization of PHE levels is required and lower levels of 60-120 $\mu\text{mol/L}$ 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
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Kuvan (sapropterin)

Medication class:

Enzyme Cofactor

FDA-approved indication(s):

- A phenylalanine hydroxylase activator indicated to reduce blood phenylalanine levels in patients with hyperphenylalaninemia caused by tetrahydrobiopterin (BH₄)-responsive phenylketonuria (PKU) in conjunction with a phenylalanine-restricted diet
- Kuvan is to be used in conjunction with a phenylalanine-restricted diet

Recommended Dose:

- Individual 1 month to 6 years
 - Starting dose is 10 mg/kg once daily
- Individual 7 years and older
 - Starting dose is 10-20 mg/kg once daily

Maximum dosage

- Not stated

Available Dosage Forms:

- 100 mg tablets, 100 mg oral powder for solution packet, 500 mg oral powder for solution packet

Warnings, Precautions, and other Clinical Information:

- Individuals whose blood phenylalanine does not decrease after 1 month of treatment at 20 mg/kg per day are non-responders, treatment with Kuvan should be discontinued in these individuals
- Kuvan is not recommended in individuals with a history of anaphylaxis to Kuvan

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- Not all individuals with PKU respond to Kuvan, response to treatment cannot be pre-determined by laboratory testing, it can only be determined by a therapeutic trial of Kuvan
- All patients with PKU who are being treated with Kuvan should also be treated with a phenylalanine-restricted diet
- Patients with liver impairment have not been evaluated in clinical trials with Kuvan, hepatic damage has been associated with impaired phenylalanine metabolism
- Use of Kuvan with drugs known to affect folate metabolism (e.g., methotrexate) and their derivatives may require more frequent monitoring of blood phenylalanine levels because these drugs can decrease endogenous BH4 levels by inhibiting the enzyme dihydropteridine reductase (DHPR)
- Monitor blood pressure when administering Kuvan with drugs that affect nitric oxide-mediated vasorelaxation (e.g., PDE-5 inhibitors such as sildenafil, vardenafil, or tadalafil), because both sapropterin dihydrochloride and PDE-5 inhibitors may induce vasorelaxation
- Use with caution when given with levodopa, individuals with underlying neurologic disorders are at risk for seizures, over-stimulation, or irritability
- The efficacy and safety of Kuvan have not been studied in neonates
- Individuals with renal impairment have not been evaluated in clinical trials

Criteria:

- **Criteria for initial therapy:** Kuvan (sapropterin dihydrochloride) is considered *medically necessary* and will be approved when **ALL** of the following criteria are met:
 1. Prescriber is 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:
 - Phenylalanine (PHE) level is above the recommended level for the individual's age or condition (baseline value must be submitted with the request)

Initial approval duration: 2 months

- **Criteria for continuation of coverage (renewal request):** Kuvan (sapropterin dihydrochloride) is considered *medically necessary* and will be approved when **ALL** of the following criteria are met:
 1. Individual continues to be seen by a specialist with knowledge and expertise in metabolic diseases or genetic diseases

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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
 - Response is 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. There are no significant interacting drugs

Renewal duration: 12 months

Resources:

Kuvan® (sapropterin). Package Insert. Revised by manufacturer 04-2014. Accessed 02-13-2015

Kuvan® (sapropterin). Package Insert. Revised by manufacturer 07-2015. Accessed 02-09-2016

Kuvan® (sapropterin). Package Insert. Revised by manufacturer 08-2016. Accessed 02-14-2017

Kuvan® (sapropterin). Package Insert. Revised by manufacturer 11-2017. Accessed 02-13-2018

Vockley J, Andersson HC, Antshel KM, et al. Phenylalanine hydroxylase deficiency: diagnosis and management guideline. Genetics in Medicine 2014 American College of Medical Genetics and Genomics Guidelines

UpToDate: Overview of phenylketonuria. Current through Jan 2018. [https://www.uptodate-com.mwu.idm.oclc.org/contents/overview-of-phenylketonuria?search=hyperphenylalaninemia&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1](https://www.uptodate.com.mwu.idm.oclc.org/contents/overview-of-phenylketonuria?search=hyperphenylalaninemia&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1)



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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
 Call 866-325-1794 to check the status of a request.
 All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
 Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.

REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information			
Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:
Prescribing Provider Information			
Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	
Dispensing Pharmacy Information			
Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:	
Requested Medication Information			
Medication Name:	Strength:	Dosage Form:	
Directions for Use:	Quantity:	Refills:	Duration of Therapy/Use:
<input type="checkbox"/> Check if requesting brand only <input type="checkbox"/> Check if requesting generic			
<input type="checkbox"/> Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)			
Turn-Around Time For Review			
<input type="checkbox"/> Standard <input type="checkbox"/> Urgent. Sign here: _____ <input type="checkbox"/> Exigent (requires prescriber to include a written statement)			
Clinical Information			
1. What is the diagnosis? Please specify below. ICD-10 Code: _____ Diagnosis Description: _____			
2. <input type="checkbox"/> Yes <input type="checkbox"/> No Was this medication started on a recent hospital discharge or emergency room visit?			
3. <input type="checkbox"/> Yes <input type="checkbox"/> No There is absence of ALL contraindications.			
4. What medication(s) has the individual tried and failed for this diagnosis? Please specify below. Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.			
Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy	
5. Are there any supporting labs or test results? Please specify below.			
Date	Test	Value	

Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: _____ Date: _____

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

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