



Kuvan® (sapropterin) Prior Authorization Criteria

FDA APPROVED INDICATIONS AND DOSAGE

FDA Indication¹: Kuvan (sapropterin) is indicated to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin-(BH4-) responsive Phenylketonuria (PKU). Kuvan is to be used in conjunction with a Phe-restricted diet.

Dosing¹: The recommended starting dose of sapropterin is 10 mg/kg once daily. Blood Phe levels should be checked after one week of therapy and periodically for one month. If blood Phe levels do not decrease after one month, the dose should be increased to 20 mg/kg daily. If blood Phe levels do not decrease after one month of therapy with 20 mg/kg daily, sapropterin should be discontinued. A responsive patient may receive a dosage within the range of 5-20 mg/kg daily.¹

CLINICAL RATIONALE

Phenylketonuria (PKU) is caused by a deficiency of the enzyme phenylalanine hydroxylase (PAH). This enzyme deficiency impairs metabolism of Phe and results in hyperphenylalaninemia (HPA). When untreated, HPA is neurotoxic and can lead to profound neurocognitive and developmental defects. Complications of PKU can be prevented with a Phe-restricted diet instituted within one week after birth.

The most commonly reported blood Phe recommendations in US clinics are 2 to 6 mg/dL for patients ≤ 12 years and 2 to 10 mg/dL for those >12 years of age. An NIH consensus panel has recommended maintenance levels of Phe as indicated in Table 2.^{2,3} In addition, given the paucity of data on the relationship between Phe level and brain function after 12 years of age and the fact that brain development continues during adolescence, even lower Phe levels (2-10 mg/dL) are strongly encouraged during this period.²

Recommended Maintenance Phenylalanine Levels for Classical PKU According to the National Institutes of Health (NIH) Consensus Statement

AGE RANGE	MAINTENANCE PHENYLALANINE LEVELS
Neonates through 12 years of age	120-360 µmol/L (2-6 mg/dL)
Greater than 12 years of age	120-900 µmol/L (2-15 mg/dL)
During pregnancy	120-360 µmol/L (2-6 mg/dL)

The NIH Consensus Statement states that a Phe-restricted diet should be implemented early in life to reduce mental deficiencies associated with PKU.² This involves use of medical foods including medical protein sources and modified low-protein products in addition to the provision of required amounts of Phe through small amounts of natural protein. Most clinics advocate lifelong dietary treatment.⁷ Resuming the diet after discontinuation is very difficult, and expertise in issues of adherence is needed. Adherence, cost of treatment, independence, and prepregnancy management become salient issues during adolescence and young adulthood.²

Several double-blind and open studies have found sapropterin to be effective in decreasing Phe concentrations in some patients. A screening trial involving 485 patients with PKU found that 20% (96/485; 95% CI 16-23%) of study patients responded to sapropterin (response defined as $\geq 30\%$ decrease in blood Phe level). A total of 89 patients who had responded to sapropterin therapy in the screening study were enrolled in a double blind, randomized, placebo controlled, six week trial. The mean change in blood Phe concentration at week six was superior in the sapropterin group ($-235.9 \pm 257 \mu\text{mol/L}$) compared to the placebo group ($2.9 \pm 239.5 \mu\text{mol/L}$) ($p < 0.0001$). A total of 80 patients who completed studies one and two above were enrolled in an open label extension study. The percentage of patients achieving a $\geq 30\%$ decrease in blood Phe concentrations was 18%, 38%, and 49% after two weeks of dosing with sapropterin 5 mg/kg, 10 mg/kg, and 20 mg/kg respectively.³

One study of sapropterin in 45 children receiving sapropterin 20mg/kg/day, showed that the mean Phe supplement tolerated with blood Phe control was 20.9 mg/kg/day, significantly greater than the pre-study allotment of 0 mg/kg/day.^{3,4}

A related trial was conducted by Trefz et al.^{3,5} It differed from the previous study population as the patients were children aged between 4 to 12 years and were adequately managing their condition through dietary control. Despite this about 50% of these patients recorded at least one Phe level $\geq 300 \mu\text{mol/L}$ in the six months prior to study commencement. As with the previous study population, the population was followed through two phases, with the latter population selected from the former. These are referred to as part 1 and part 2 respectively.^{3,5}

- Ninety patients were entered into part 1 with efficacy based on the results of 89 patients. This was an open label study of eight days' duration using a treatment dose of 20 mg/kg. The objective of this part of the study was to identify treatment responders for randomization into part 2. Responders were defined on the basis of a reduction in Phe levels $\geq 30\%$ and with a Phe level $< 300 \mu\text{mol/L}$. Fifty patients were subsequently classified as responders (56%).
- Part 2 was a 10 week, phase III, randomized, placebo-controlled study in 46 patients from part 1 who were identified as responders (mean age 8 years, 58% male). The objective of part 2 of the study was to investigate whether sapropterin could increase dietary Phe tolerance and thereby permit a less restrictive and more palatable diet for patients with PKU. Patients were randomized at a ratio of 3:1 resulting in 33 allocated to sapropterin 20 mg/kg and 12 to placebo daily (one patient did not receive any treatment and was excluded from efficacy analyses). Efficacy was determined on the quantity of Phe supplementation that each patient could tolerate with tolerance defined as a Phe level $< 360 \mu\text{mol/L}$. In the sapropterin group 11 patients (33%) could tolerate the maximum permitted level of Phe supplementation of 50 mg/kg/day, with ten patients (30%) tolerating 10 to 30 mg/kg/day, seven tolerating 1 to 10 mg/kg/day and five not able to tolerate any Phe supplementation. In the placebo group no patient could tolerate more than 10 mg/kg/day. The adjusted mean Phe supplement tolerated for sapropterin was 21 mg/kg/day vs. 3 mg/kg/day with placebo ($p < 0.001$).^{3,5}

Some clinicians believe that one goal of therapy with sapropterin may be to liberalize the diet with increased Phe tolerance.⁶

Not all patients with PKU respond to treatment with sapropterin. In clinical trials, approximately 20% to 56% of PKU patients responded to treatment with sapropterin. Response to treatment cannot be predetermined by laboratory testing (e.g. genetic testing), and can only be determined by a therapeutic trial of sapropterin. Patients with PKU who are being treated with sapropterin should also be treated with a Phe restricted diet. The initiation of sapropterin therapy does not eliminate the need for appropriate monitoring by trained

professionals to assure that blood Phe control is maintained in the context of ongoing dietary management.^{1,3}

For additional clinical information see Prime Therapeutics Formulary Chapter 4.9M: Metabolic Modifiers.

REFERENCES

1. Kuvan prescribing information. BioMarin Pharmaceutical Inc. December 2007.
2. Phenylketonuria: Screening and Management. NIH Consensus Statement Online 2000 October 16-18;17(3):1-27. Accessed April 19, 2010 at: <http://consensus.nih.gov/2000/2000phenylketonuria113html.htm>.
3. Prime Therapeutics Formulary Chapter 4.9M: Metabolic Modifiers. July 2009.
4. Sapropterin managed care dossier. Biomarin Pharmaceuticals Inc. January 2008.
5. Trefz FK, Burton BK, Longo N, et al. Efficacy of sapropterin dihydrochloride in increasing phenylalanine tolerance in children with phenylketonuria: a phase III, randomized, double-blind, placebo-controlled study. *J Pediatr.* 2009;154:700-707.
6. Burton BK. Consultation for Kuvan (personal communication with Prime Therapeutics National Pharmacy and Therapeutics Committee). August 2008.
7. Hoeks MPA, den Heiger M, Janssen MCH. Adult issues in phenylketonuria. *Neth J Med.* 2009;67(1):2-7

Document History

Original Prime Standard criteria approved by P&T UM Committee 02/2009

Original Client Specific criteria approved by HCSC Corporate Clinical Committee 05/2009

Annual Review Prime Standard criteria, criteria maintained, approved by P&T UM Committee 02/2010

Client Annual Review Client Specific criteria with changes approved by HCSC Corporate Clinical Committee 06/2010

Kuvan® (sapropterin) Prior Authorization

OBJECTIVE

The intent of the Kuvan (sapropterin) Prior Authorization (PA) program is to appropriately select patients for treatment according to product labeling and/or clinical studies and/or clinical practice guidelines. The PA criteria consider Kuvan appropriate for use in patients who: a) have been diagnosed with PKU, b) have a baseline blood Phe measured shortly prior to initiating therapy, c) are unable to maintain Phe levels within the recommended range despite compliance with dietary restrictions, and d) are able to maintain a consistent Phe-restricted diet during a Kuvan trial period. The PA criteria also require that the prescriber be a specialist with knowledge and expertise in metabolic diseases or genetic diseases. Initial approval will be for two months of therapy if the initial dose is 5-10 mg/kg/day; it will be for one month if the initial dose is 20 mg/kg/day. Additional (renewal) approvals for continued use will be for 6 months if patient response is seen. Patient response is defined as a $\geq 30\%$ decrease in blood Phe level from baseline or the maintenance of blood Phe level within recommended range.

TARGET DRUGS

Kuvan® (sapropterin)

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Kuvan will be approved for INITIAL USE when ALL of the following are met:

1. The patient has NOT been previously treated with Kuvan **AND**
2. The patient has a diagnosis of phenylketonuria (PKU) **AND**
3. The patient is on a phenylalanine (Phe) restricted diet **AND**
4. The prescriber has submitted a baseline blood Phe level measured within 2 weeks prior to initiation of Kuvan therapy which is above the recommended levels indicated for the patient's age range or condition **AND**
5. The prescriber has verified that the patient's diet will NOT be modified in any way during the initial 1-month or 2-month trial of Kuvan therapy **AND**
6. The prescriber is a specialist with knowledge and expertise in metabolic diseases or genetic diseases **AND**
7. The dose is within the FDA-labeled dose range of 5 to 20 mg/kg/day

Length of Approval: for 2 months if initial dose is 5-10/mg/kg/day;
for 1 month if initial does is 20 mg/kg/day.

Kuvan will be approved for RENEWAL when ALL of the following are met:

1. The patient has been previously treated with Kuvan **AND**
2. The patient been successfully treated with Kuvan (sapropterin) as defined by one of the following:
 - a. The patient's blood Phe levels are being maintained within the acceptable range **OR**
 - b. The patient has had $\geq 30\%$ decrease in blood Phe level from baseline **AND**
3. The prescriber has verified that the patient's diet was NOT modified in any way during the initial 1-month or 2-month trial of Kuvan therapy **AND**
4. The prescriber a specialist with knowledge and expertise in metabolic diseases or genetic diseases **AND**
5. The dose is within the FDA-labeled dose range of 5 to 20 mg/kg/day

Length of Approval: 6 months

Kuvan® (sapropterin) Prior Authorization

ELECTRONIC EDIT

The overall process for a prior authorization will not allow the targeted drugs to adjudicate through the claims system. When a patient requests a targeted drug the system will reject the claim with the message indicating that prior authorization is necessary.

Brand (generic)	GPI	Multisource Code
Kuvan® (sapropterin)		
100 mg tablet	30908565107320	M, N, O, or Y

PRIOR AUTHORIZATION CRITERIA QUESTION SET

Initial Evaluation

1. Has the patient been previously treated with Kuvan (sapropterin)?
If yes, Renewal Evaluation applies. If no, continue to 2.
2. Has the patient been diagnosed with phenylketonuria (PKU)?
If yes, continue to 3. If no, deny.
3. Has the prescriber verified that the patient is on a phenylalanine (Phe) restricted diet?
If yes, continue to 4. If no, deny.
4. Has the prescriber submitted a baseline blood Phe level measured within 2 weeks prior to initiation of Kuvan therapy?
If yes, continue to 5. If no, deny.
5. Is the Phe level submitted above the recommended levels indicated for the patient's age range or condition in the table above?
If yes, continue to 6. If no, deny.
6. Has the prescriber verified that the patient's diet will NOT be modified in any way during the initial 1-month or 2-month trial of Kuvan therapy?
If yes, continue to 7. If no, deny.
7. Is the prescriber a specialist with knowledge and expertise in metabolic diseases or genetic diseases?
If yes, continue to 8. If no, deny.
8. Is the requested dose within the FDA-labeled dose range of 5 to 20 mg/kg/day?
If yes, approve: for 2 months if initial dose is 5-10/mg/kg/day;
for 1 month if initial does is 20 mg/kg/day.
If no, deny.

Renewal Evaluation

1. Has the patient been previously treated with Kuvan (sapropterin)?
If yes, continue to 2. If no, Initial Evaluation applies.
2. Has the patient been successfully treated with Kuvan (sapropterin) as defined by one of the following?
 - a. Patient's blood Phe levels are being maintained within the acceptable range (see Table 2) OR
 - b. Patient has had $\geq 30\%$ decrease in blood Phe level from baselineIf yes, continue to 3. If no, deny.
3. Has the prescriber verified that the patient's diet was NOT modified in any way during the initial 1-month or 2-month trial of Kuvan therapy?
If yes, continue to 4. If no, deny.
4. Is the prescriber a specialist with knowledge and expertise in metabolic diseases or genetic diseases?
If yes, continue to 5. If no, deny.
5. Is the requested dose within the FDA-labeled dose range of 5 to 20 mg/kg/day?
If yes, approve for 6 months. If no, deny.