IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Sapropterin (Kuvan) is an orally administered medication used in conjunction with a phenylalanine (Phe) restricted diet to reduce blood phenylalanine levels in patients with phenylketonuria (PKU).
Policy/Criteria

I. Most contracts require prior authorization approval of sapropterin (Kuvan) prior to coverage. Sapropterin (Kuvan) may be considered medically necessary when ALL criteria (A, B, and C) below are met.

A. A diagnosis of phenylketonuria (PKU) has been established by a metabolic specialist.

AND

B. Phenylalanine (Phe) levels cannot be maintained within the recommended maintenance range [120-360 µmol/dL (2 – 6 mg/dL)] with dietary intervention alone.

AND

C. Documentation of an elevated average baseline blood Phe level, prior to initiating therapy with sapropterin (Kuvan) and a current body weight.

II. Administration, Quantity Limitations, and Authorization Period

A. OmedaRx considers sapropterin (Kuvan) to be a self-administered medication.

B. When prior authorization is approved, sapropterin (Kuvan) may be covered in quantities as follows:
   1. Up to 10 mg/kg/day for up to two months.
   2. Up to 20 mg/kg/day for up to two months, when there is clinical documentation that current treatment with sapropterin (Kuvan) 10 mg/kg/day is not effective after at least 8 days of sapropterin (Kuvan) treatment, defined as less than a 30% decrease in blood Phe level from baseline (the Phe level provided in criterion I.C. above).

   NOTE: Number of tablets (or powder packets for solution) authorized per month will be rounded to the nearest 100 mg. Doses exceeding 20 mg/kg/day are considered investigational.

C. Authorization shall be reviewed at least every six months to confirm that that current medical necessity criteria are met and that the medication is effective, by confirmation of ALL of the following (1,2, AND 3):
   1. The blood Phe level has decreased at least 30% from baseline (the Phe level provided in criterion I.C. above).
   2. The patient remains compliant with a phenylalanine-restricted diet, based on clinical documentation.
   3. The dose of sapropterin (Kuvan) does not exceed 20 mg/kg/day, based on the patient’s recent weight (within the last 90 days). All doses will be rounded to the nearest 100 mg.
III. Sapropterin (Kuvan) is considered investigational when used for any condition other than phenylketonuria, including, but not limited to autism and cirrhosis with portal hypertension.

Position Statement

- Sapropterin (Kuvan) is approved for the reduction of blood phenylalanine (Phe) levels in patients with high Phe levels (hyperphenylalaninemia) due to tetrahydrobiopterin (BH4)-responsive phenylketonuria (PKU), despite dietary intervention. Sapropterin (Kuvan) is to be used in conjunction with a Phe-restricted diet.

- Sapropterin (Kuvan) is a synthetic form of BH4, a cofactor required for metabolism of Phe to tyrosine. Without this cofactor, excess Phe accumulates in the blood and tissues. Sapropterin (Kuvan) is the first medication indicated for the treatment of PKU.

- Untreated PKU is associated with severe mental retardation, reduced IQ scores, behavioral difficulties and other symptoms. However, there is no consensus concerning the optimal blood Phe level. In addition, the blood Phe concentration associated with optimal central nervous system outcomes is uncertain.

- Although there is evidence that sapropterin (Kuvan) lowers blood Phe levels in patients with PKU, the long-term impact of sapropterin (Kuvan) on neurological development is unknown. There is no evidence to indicate that sapropterin (Kuvan) improves long-term patient outcomes.

- The standard treatment for patients with PKU is maintaining a diet with a low Phe content. Guidelines indicate that sapropterin (Kuvan) may be useful in reducing Phe levels in responsive patients, but experience in patients under the age of four is limited. Any combination of therapies that facilitate improvement in blood Phe levels for a given individual is appropriate; therapies may be combined and should be individualized.

- In clinical trials, patients were considered responders to sapropterin (Kuvan) if blood Phe levels decreased at least 30% from baseline. A response was seen as early as eight days after initiating treatment.

- The recommended starting dose of sapropterin (Kuvan) is 10 mg/kg/day taken once daily. For patients who do not respond, the dose can be increased to 20 mg/kg/day. The efficacy and safety of higher doses has not been established.

- If blood Phe levels do not decrease after one month of treatment (“non-responders”), treatment with sapropterin (Kuvan) should be discontinued.

- Sapropterin (Kuvan) is available through limited distribution.

Clinical Efficacy

- The efficacy of sapropterin (Kuvan) was established based on five clinical trials: one open-label trial [2] with a follow-on randomized controlled trial [3] and open-label extension trial [4], as well as two additional Phase 3 trials. [1,5]

  * Sapropterin (Kuvan) was dosed at 10 to 20 mg/kg/day.
  
  * The study duration ranged from eight days to 22 weeks.
  
  * The primary efficacy endpoint was the change in blood Phe concentration from baseline.
“Responders” were defined as patients who achieved at least a 30% decrease in blood Phe levels with sapropterin (Kuvan) treatment.

- Based on the clinical trial evidence, two high quality systematic reviews concluded treatment with sapropterin (Kuvan) decreases Phe blood levels. [6,7]

- One systematic review found Phe levels were reduced by at least 30% in up to half of sapropterin (Kuvan) treated patients (32 to 50%). [7]

- The other systematic review found a decrease in Phe levels versus baseline in sapropterin (Kuvan) treated patients. The average reduction in those on a Phe-restricted diet was a non-statistically significant change of -51.90 μmol/L. The average reduction in those on a relaxed or abandoned Phe-restricted diet, was a statistically significant change of -238.80 μmol/L. [6]

- PKU treatment aims to maintain blood Phe levels within recommended ranges (See Appendix I), to prevent neurologic damage; however, the blood Phe concentration associated with optimal neurodevelopmental outcome is uncertain. [6,8]

- There are no studies comparing the use of sapropterin (Kuvan) to a Phe-restricted diet.

- There is insufficient data to make a conclusion regarding the impact of sapropterin (Kuvan) for improving clinically meaningful outcomes such as executive function (i.e. cognition). [6,7]

- One small case series, sited within a systematic review, reported on intelligence quotient (IQ) and nutritional outcomes. After 1 year on sapropterin (Kuvan) 5mg/kg/day, the 11 participants discontinued use of a medical food and began a normal diet. IQ scores after 12 months on sapropterin (Kuvan) were similar to scores before treatment and development quotients were within normal limits. [7]

- There are no studies which evaluate sapropterin (Kuvan) treatment for quality-of-life outcomes. [6,7]

- There is insufficient data to make a conclusion regarding the impact of sapropterin (Kuvan) in the treatment of severe PKU. [8]

- Currently there are no other medications used in the treatment of PKU, so comparison to other medications is not possible.

- The two systematic reviews also evaluated the overall treatment of patients with PKU. [6,7]

- The mainstay of PKU treatment is a Phe-restricted diet, ideally continued into adult life, with regular monitoring of blood Phe levels. Patients often require dietary supplements in the form of medical foods containing low-Phe protein sources.

- Non-compliance to the restricted diet in teenagers and adults show subtle cognitive impairments relative to controls and is associated with an increase in the rate of eczema, asthma, mental disorders, headache, hyperactivity, and hypoactivity.
There are no definitive studies on the effects of dietary treatment in adults, but individual case reports have documented deterioration of adult PKU patients after diet discontinuation.

In addition, there is a lack of information on how much improvement might be expected on Phe levels with such a diet.

Given the variability of genetic deficiency found with hyperphenylalaninemia, patients whose blood Phe does not decrease after 1 month despite the maximum sapropterin (Kuvan) daily dose of 20 mg/kg/day are “non-responders,” and treatment with sapropterin (Kuvan) should be discontinued in these patients. [1]

To achieve metabolic control, guidelines recommend use of a Phe-restricted diet, including medical foods and low-protein products, as the standard of care for almost all individuals with classical PKU for their entire lifetime. Some relaxation may be tolerable, in some cases, as the individual ages.

Treatment guidelines recognize sapropterin (Kuvan) as the only FDA-approved medication for phenylketonuria which may be useful in reducing Phe levels in responsive patients. Response to sapropterin (Kuvan) is not accurately predicted by genotype and thus should be documented by formal testing. The primary goal of therapy is to lower blood Phe, and any interventions, including dietary restrictions, medical foods, or pharmacotherapy that help achieve that goal without other negative consequences, should be considered appropriate therapy. Patient response to each intervention is variable and choice of treatment should be individualized.

Sapropterin (Kuvan) did not improve hepatic venous pressure gradient in subjects with cirrhosis and portal hypertension. [10]

Sapropterin (Kuvan) did not improve Clinical Global Impressions Improvement (CGI-I) or Severity (CGI-S) in patients with autism spectrum disorders. [11]

Safety [1]

The most common side effects observed in clinical trials include headache, upper respiratory infection, rhinorrhea, pharyngolaryngeal pain, diarrhea, nausea and vomiting.

The most serious adverse reactions during sapropterin (Kuvan) administration (regardless of relationship to treatment) were gastritis, spinal cord injury, streptococcal infection, testicular carcinoma, and urinary tract infection.

The safety and efficacy of sapropterin (Kuvan) in children under the age of one month has not been established.

Children less than 7 years of age should be started on lower doses of sapropterin (Kuvan) of 10 mg/kg/day to prevent abnormally low blood Phe levels. Doses may be titrated to 20 mg/kg/day, as needed, for blood Phe level reduction.

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References


Revision History

<table>
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<th>Revision Summary</th>
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<tr>
<td>09/8/2017</td>
<td>No criteria changes with this annual review.</td>
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<tr>
<td>08/12/2016</td>
<td>Investigational uses clarified to include cirrhosis and portal hypertension.</td>
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