sapropterin dihydrochloride (Kuvan)®

Policy # 00303
Original Effective Date: 08/17/2011
Current Effective Date: 09/14/2020

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of sapropterin dihydrochloride (Kuvan)®‡ for the treatment of hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4-) responsive phenylketonuria (PKU) to be **eligible for coverage**.**

Patient Selection Criteria
Coverage eligibility for the use of sapropterin dihydrochloride (Kuvan) for the treatment of HPA will be considered when both of the following criteria are met:

- Patient has diagnosis of HPA due to BH4- PKU; and
- Patient is on a phenylalanine (Phe) restricted diet.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of sapropterin dihydrochloride (Kuvan) when patient selection criteria are not met to be **investigational.***

Background/Overview

Kuvan is a synthetic preparation of naturally occurring BH4-, which is a cofactor for the enzyme phenylalanine hydroxylase (PAH). PAH hydroxylates Phe through an oxidative reaction to form tyrosine. In patients with PKU, PAH activity is deficient or absent. Treatment with BH4- can activate

residual PAH enzyme, improve the normal oxidative metabolism of Phe, and decrease Phe levels in some patients. In patients with PKU who are responsive to treatment, blood Phe levels decrease within 24 hours after administration, although maximal effect on Phe levels may take up to one month. In 8-day and 6-week pivotal trials, response to Kuvan treatment was defined as ≥ 30% decrease in blood Phe concentration from baseline. However, in some cases (e.g., patients with mild HPA, neonates or children <4 years of age, or pregnant women), a 20% reduction in blood Phe concentration may be sufficient. Kuvan is supplied as 100mg tablets. The recommended starting dose of Kuvan is 10mg/kg/day taken once daily. Doses of Kuvan may be adjusted in the range of 5-20mg/kg taken once daily. Doses of Kuvan above 20mg/kg/day have not been evaluated.

Phenylketonuria

PKU is an autosomal recessive disorder caused by a defect in PAH. Kuvan is a synthetic formulation of BH4-. BH4- has many roles in the body. One of which is to convert amino acids, such as Phe, to precursors of serotonin and dopamine via PAH. The lack of BH4- could result in PKU from HPA. This buildup could lead to severe brain damage, behavioral abnormalities, mental retardation, speech impediments, etc. Kuvan works in the body to supplement the BH4-, which in turn helps to convert Phe via PAH appropriately and therefore lowers the levels of Phe in the blood.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

In December 2007, the U.S. FDA granted marketing approval for Kuvan (sapropterin dihydrochloride) tablets, the first specific drug therapy approved to reduce blood Phe levels in patients with HPA due to BH4-responsive PKU.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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Kuvan was studied in four clinical trials. Study 1 was a multicenter, open-label, uncontrolled clinical trial of 489 patients with PKU, ages 8 to 48 years (mean 22 years), who had baseline blood Phe levels ≥450 μmol/L and who were not on Phe-restricted diets. All patients received treatment with Kuvan 10mg/kg/day for 8 days. For the purposes of this study, response to Kuvan treatment was defined as a ≥30% decrease in blood Phe from baseline. At Day 8, 96 patients (20%) were identified as responders.

Study 2 was a multicenter, double-blind, placebo-controlled study of 88 patients with PKU who responded to Kuvan in Study 1. After a washout period from Study 1, patients were randomized equally to either Kuvan 10mg/kg/day (N=41) or placebo (N=47) for 6 weeks. Efficacy was assessed by the mean change in blood Phe level from baseline to Week 6 in the Kuvan-treated group as compared to the mean change in the placebo group. The results showed that at baseline, the mean standard deviation (±SD) blood Phe level was 843 (±300) μmol/L in the Kuvan-treated group and 888 (±323) μmol/L in the placebo group. At Week 6, the Kuvan-treated group had a mean (±SD) blood Phe level of 607 (±377) μmol/L, and the placebo group had a mean blood Phe level of 891 (±348) μmol/L. At Week 6, the Kuvan- and placebo-treated groups had mean changes in blood Phe level of –239 and 6 μmol/L, respectively (mean percent changes of –29% (±32) and 3% (±33), respectively). The difference between the groups was statistically significant ($p<0.001$).

Study 3 was a multicenter, open-label, extension study in which 80 patients who responded to Kuvan treatment in Study 1 and completed Study 2 underwent 6 weeks of forced dose-titration with 3 different doses of Kuvan. Treatments consisted of 3 consecutive 2-week courses of Kuvan at doses of 5, then 20, and then 10 mg/kg/day. Blood Phe level was monitored after 2 weeks of treatment at each dose level. At baseline, mean (±SD) blood Phe was 844 (±398) μmol/L. At the end of treatment with 5, 10, and 20 mg/kg/day, mean (±SD) blood Phe levels were 744 (±384) μmol/L, 640 (±382) μmol/L, and 581 (±399) μmol/L, respectively.

Study 4 was a multicenter study of 90 children with PKU, ages 4 to 12 years, who were on Phe-restricted diets and who had blood Phe levels ≤480μmol/L at screening. All patients were treated with open-label Kuvan 20 mg/kg/day for 8 days. Response to Kuvan was defined as a ≥30% decrease in blood Phe from baseline at Day 8. At Day 8, 50 patients (56%) had a ≥30% decrease in blood Phe.

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References

1. Kuvan tablets package insert. Novato, CA: BioMarin Pharmaceuticals; April 2014.
2. Drugs at FDA. Sapropterin (Kuvan).

Policy History

Original Effective Date: 08/17/2011
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08/04/2011	Medical Policy Committee review
08/17/2011	Medical Policy Implementation Committee approval. New policy.
08/02/2012	Medical Policy Committee review
08/15/2012	Medical Policy Implementation Committee approval. No change to coverage.
02/19/2013	Coding updated
08/01/2013	Medical Policy Committee review
08/21/2013	Medical Policy Implementation Committee approval. Reworded the patient selection criteria, however there is no coverage change. Added background on phenylketonuria. Changed the rationale/source section to info from the package insert regarding the clinical trials.
08/07/2014	Medical Policy Committee review
08/20/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/06/2015	Medical Policy Committee review
08/19/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/04/2016	Medical Policy Committee review
08/17/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2017	Medical Policy Committee review
08/23/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/09/2018	Medical Policy Committee review
08/15/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/01/2019	Medical Policy Committee review

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08/14/2019 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/06/2020 Medical Policy Committee review
08/12/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date: 08/2021

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

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C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.