Clinical Policy: Sapropterin Dihydrochloride (Kuvan)

Reference Number: CP. PHAR.43
Effective Date: 02.01.10
Last Review Date: 05.20 Revision Log
Line of Business: Commercial, HIM, Medicaid

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Sapropterin dihydrochloride (Kuvan®) is a synthetic form of tetrahydrobiopterin (BH4), the cofactor for the enzyme phenylalanine hydroxylase.

FDA Approved Indication(s)
Kuvan is indicated to reduce blood phenylalanine (Phe) levels in adult and pediatric patients one month of age and older with hyperphenylalaninemia (HPA) due to BH4-responsive phenylketonuria (PKU). Kuvan is to be used in conjunction with a Phe-restricted diet.

Policy/Criteria
Provider must submit documentation (including such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Kuvan is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Phenylketonuria (must meet all):

1. Diagnosis of HPA due to PKU;
2. Prescribed by or in consultation with a metabolic or genetic disease specialist;
3. Recent (within 90 days) Phe blood level is > 360 µmols/L;
4. Dose does not exceed 20 mg per kg per day.

Approval duration: 3 months

B. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Phenylketonuria (must meet all):

1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
2. Member is responding positively to therapy as demonstrated by a reduction in Phe blood levels since initiation of therapy;
3. If request is for a dose increase, new dose does not exceed 20 mg per kg per day.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

BH4: tetrahydrobiopterin
HPA: hyperphenylalaninemia
Phe: phenylalanine
PKU: phenylketonuria

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

None reported

Appendix D: General Information

- According to the Prescribing Information, if a 10 mg/kg per day starting dose is used, then response to therapy is determined by change in blood Phe following treatment with Kuvan at 10 mg/kg per day for a period of up to 1 month. Blood Phe levels should be checked after 1 week of Kuvan treatment and periodically for up to a month. If blood Phe does not decrease from baseline at 10 mg/kg per day, the dose may be increased to 20 mg/kg per day. Additionally, regardless of starting dose, patients whose blood Phe does not decrease after 1 month of treatment at 20 mg/kg per day are non-responders and treatment with Kuvan should be discontinued in these patients.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
BH4-responsive PKU	Age 1 month to ≤ 6 years (starting dose) 10 mg/kg PO QD Age ≥ 7 years (starting dose): 10 to 20 mg/kg PO QD	20 mg/kg/day

VI. Product Availability

Tablets: 100 mg
Powder for oral solution: 100 mg, 500 mg

VII. References

1. Kuvan Prescribing Information. Novato, CA: BioMarin Pharmaceutical, Inc.; December 2019. Available at www.Kuvan.com. Accessed February 20, 2020.
2. Levy HL, Milanowski A, Chakrapani A, et. al. Efficacy of sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH4) for reduction of phenylalanine concentration in patients with phenylketonuria: a phase III randomised placebo-controlled study. Lancet. 2007;370(9586):504.
3. Vockly J, Andersson HC, Antshel KM, et al. ACMG practice guidelines: phenylalanine hydroxylase deficiency: diagnosis and management guideline. Genet Med. 2014; 16(2): 188-200.
4. Camp KM, Parisi MA, Acosta PB, et al. Phenylketonuria scientific review conference: state of the science and future research needs. Mol Genet Metab. June 2014; 112(2): 87-122.
5. van Spronsen FJ. Mild hyperphenylalaninemia: to treat or not to treat. J Inherit Metab Dis. 2011; 34: 651-656.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy converted to new template. Initial criteria: Removed requests for documentation; specialist criteria added given complexity of disease state and recommendation for multidisciplinary management[2-4]; added max dose per PI. Removed baseline Phe requirement of >600 µmol/L if >12 years; added contraindications, including two null mutations per guidelines.[2-3] Changed initial approval duration to two months; changed requirement that Phe decrease to 120–360 µmol/l during the Kuvan trial period to "any Phe decrease."	03.01.16	04.16
Removed contraindication of anaphylaxis to Kuvan due to verification challenges; Added a time frame for which Phe level will be considered valid.	03.01.17	04.17
1Q18 annual review: - The diagnostic description "BH4 responsive" in relation to PKU is deleted as it may not be determined until after a therapeutic trial. - Use in conjunction with a Phe-restricted diet is removed. - Initial approval duration increased from 2 to 3 months to allow adequate time for follow-up. Continuation criteria that refers to an increase in dietary Phe tolerance or improvement in neuropsychiatric symptoms is deleted leaving reduction of Phe levels per the PI. - References reviewed and updated.	11.17.17	02.18

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2019 annual review: HIM line of business added; no significant changes; references reviewed and updated.	11.13.18	02.19
Added Commercial line of business.	02.19.19	05.19
2Q 2020 annual review: no significant changes; references reviewed and updated.	02.20.20	05.20

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.