Clinical Policy: Sapropterin Dihydrochloride (Kuvan, Javygtor, Zelvysia)

Reference Number: CP.PHAR.43
Effective Date: 02.01.10
Last Review Date: 05.26
Line of Business: Commercial, HIM/ICHRA, Medicaid Revision Log

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 tetrahydrobiopterin- (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 and sapropterin formulations are **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 an endocrinologist, metabolic or genetic disease specialist;
3. Recent (within 90 days) Phe blood level is > 360 µmols/L;
4. Member is currently adherent on a Phe-restricted diet and will continue this diet during treatment with sapropterin;
5. Sapropterin is not prescribed concurrently with Palynziq® or Sephience™;
6. If request is for brand Kuvan, Javygtor, or Zelvysia, member must use generic sapropterin, unless contraindicated or clinically significant adverse effects are experienced;
7. Documentation of member's current weight (in kg);
8. Dose does not exceed 20 mg/kg per day.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):

a. For drugs on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace/ICHRA, and CP.PMN.255 for Medicaid; or
b. For drugs NOT on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace/ICHRA, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace/ICHRA, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Phenylketonuria (must meet all):

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy as demonstrated by a reduction in Phe blood levels since initiation of therapy;
3. Member is currently adherent on a Phe-restricted diet and will continue this diet during treatment with Kuvan;
4. If request is for brand Kuvan, Javygtor, or Zelvysia, member must use generic sapropterin, unless contraindicated or clinically significant adverse effects are experienced;
5. Sapropterin is not prescribed concurrently with Palynziq or Sephience;
6. Documentation of member's current weight (in kg);
7. If request is for a dose increase, new dose does not exceed 20 mg/kg per day.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace/ICHRA, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the non-formulary policy for the

relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace/ICHRA, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace/ICHRA, 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. PA.154 for health insurance marketplace/ICHRA, CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

BH4: tetrahydrobiopterin
FDA: Food and Drug Administration
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

- Tablet: 100 mg
- Powder for oral solution: 100 mg, 500 mg

VII. References

1. Kuvan Prescribing Information. Novato, CA: BioMarin Pharmaceutical, Inc.; August 2024. Available at www.Kuvan.com. Accessed January 14, 2026.
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 randomized 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.
6. Smith WE, Berry SA, Bloom K, et al. Phenylalanine hydroxylase deficiency diagnosis and management: a 2023 evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). Genetics in Medicine. 2024;27(1):101289. doi: https://doi.org/10.1016/j.gim.2024.101289.
7. Van Wegberg AMJ, MacDonald A, Ahring K, et al. European guidelines on diagnosis and treatment of phenylketonuria: first revision. Molecular Genetics and Metabolism. June 2025;145(2):109125. https://doi.org/10.1016/j.ymgme.2025.109125.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
2Q 2022 annual review: no significant changes; added redirection to generic product for brand requests; references reviewed and updated.	02.27.22	05.22
Template changes applied to other diagnoses/indications and continued therapy section.	11.23.22	
2Q 2023 annual review: no significant changes; references reviewed and updated.	02.09.23	05.23
2Q 2024 annual review: increased initial auth duration to align with those of other drugs for rare diseases; for Continued Therapy added exclusion for concomitant use with Palynziq to match with the Initial Approval Criteria; references reviewed and updated.	02.29.24	05.24
2Q 2025 annual review: no significant changes; added requirement for a redirection from Javygtor (branded generic) to unbranded generic sapropterin per an SDC recommendation; added a requirement for documentation of member's current weight for dose calculation purposes; references reviewed and updated.	03.10.25	05.25
Added Sephience (newly FDA-approved for PKU) as an agent that should not be used concomitantly with sapropterin; extended initial approval duration to 12 months; references reviewed and updated.	08.28.25	11.25

Reviews, Revisions, and Approvals	Date	P&T Approval Date
2Q 2026 annual review: no significant changes; added requirement for a redirection from Zelvysia (another branded generic) to unbranded generic sapropterin; added endocrinologist as a possible specialist to align with the Palynziq and Sephience criteria; added adherence to Phe-restricted diet per plan feedback and align with Sephience criteria; references reviewed and updated. Added ICHRA line of business.	04.10.26	05.26

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.