Drug Coverage Policy

Effective Date.....11/01/2025
Coverage Policy Number.....IP0295
Policy Title.....Phenylketonuria – Sapropterin

Phenylketonuria – Sapropterin

- Kuvan™ (sapropterin dihydrochloride tablets and powder for oral solution – BioMarin, generic)
- Javygtor™ (sapropterin dihydrochloride tablets and powder for oral solution – Dr. Reddy's Laboratories)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

OVERVIEW
Sapropterin (Kuvan, Javygtor, generic), a synthetic form of the cofactor for the enzyme phenylalanine hydroxylase, is indicated to reduce blood phenylalanine levels in patients one month of age and older with hyperphenylalaninemia due to tetrahydrobiopterin-responsive **phenylketonuria (PKU).**[1]

The medication should be used with a phenylalanine-restricted diet. Of note, some patients do not show a biochemical response to sapropterin. Per the prescribing information, biochemical response cannot generally be predetermined by laboratory testing and should be determined through a therapeutic trial (evaluation) of sapropterin response.

Dose Titration
The initial starting dose of sapropterin is either 10 mg/kg per day or 20 mg/kg per day. If a 10 mg/kg per day starting dose is used, the dose should be increased to 20 mg/kg if the patient's blood phenylalanine does not decrease after 1 month of treatment. If blood phenylalanine does not decrease after 1 month of treatment on 20 mg/kg per day, sapropterin should be discontinued.

In clinical trials, 20% to 61% of patients enrolled were responsive to sapropterin (defined as reduction in blood phenylalanine (Phe) by $\geq$ 30% from baseline).[1] A lower degree of responsiveness (e.g., 20%) might be considered sufficient in some individuals.[2]

Overview
PKU or phenylalanine hydroxylase (PAH) deficiency is an autosomal recessive disorder caused by pathogenic variants in the *PAH* gene.[3] PAH converts Phe to tyrosine and requires the co-substrate tetrahydrobiopterin (BH_4). With PAH deficiency, Phe can accumulate and lead to brain dysfunction resulting in severe intellectual disability, epilepsy, and behavioral problems. The incidence of PKU in the United States is approximately 1 in 25,000, which equates to approximately 13,600 individuals living with PKU.[4]

Guidelines
In 2023, the American College of Medical Genetics and Genomics (ACMG) updated their practice guidelines for the diagnosis and management of PAH deficiency.[5] ACMG recommends treating individuals with blood Phe levels > 360 µmol/L and maintaining Phe levels to $\leq$ 360 µmol/L for life as it is associated with higher intelligence quotient (IQ) levels. ACMG advocates combination of therapies (e.g., dietary restriction, use of medical foods that are Phe-free or low in Phe, sapropterin, Palynziq) and individualization of treatment to improve blood Phe levels. Therapy resulting in a reduction of blood Phe, increase in dietary Phe tolerance, or improvement in clinical symptoms should be continued. In addition, sapropterin is conditionally recommended in pregnant individuals to achieve maternal Phe levels $\leq$ 360 µmol/L to prevent negative gestational outcomes or negative outcomes for the offspring.

European guidelines (2025) are available for diagnosis and management of PKU.[6] The guidelines classify PKU as either not requiring treatment (Phe < 360 µmol/L), requiring treatment and co-factor (i.e., sapropterin) responsive, or requiring treatment and co-factor non-responsive. Early treatment is advocated (ideally before 10 days of age), and children < 12 years of age should aim for a Phe level of 120 to 360 µmol/L. However, unlike the US guidelines, the target level for children $\geq$12 to 18 years old and for adults > 18 years old is higher at 120 to 600 µmol/L (except in pregnancy where the target level is 120 to 360 µmol/L). Sapropterin is discussed as a treatment option with recommendations provided for identifying potential responders, such as genotype analysis or a sapropterin loading test. However, it is noted that long-term response should be proven in a treatment trial.

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POLICY STATEMENT
Prior Authorization is required for benefit coverage of sapropterin (Kuvan, Javygtor, generic). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with sapropterin as well as the monitoring required for adverse events and long-term efficacy, initial approval requires sapropterin to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information.

Sapropterin (Javygtor, Kuvan, generic) are considered medically necessary when the following are met:

FDA-Approved Indication

1. **Phenylketonuria.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A.** Initial Therapy. Approve for 12 weeks if the patient meets ALL of the following (i, ii and iii):
     - **i.** The medication is prescribed in conjunction with a phenylalanine-restricted diet; AND
     - **ii.** The medication is prescribed by, or in consultation with, a metabolic disease specialist (or specialist who focuses on the treatment of metabolic diseases); AND
     - **iii.** Preferred product criteria is met for the product(s) as listed in the below table(s); OR
   - **B.** Patients is Currently Receiving Sapropterin (Kuvan, Javygtor, generic). Approve for 1 year if the patient meets BOTH of the following (i and ii):
     Note: A patient who has received < 12 weeks of therapy or who is restarting therapy with sapropterin should be considered under Initial Therapy.
     - **i.** Patient meets ONE of the following (a, b, or c):
       - **a.** According to the prescriber, patient has had a clinical response; OR
         Note: Examples of clinical response may include cognitive and/or behavioral improvements.
       - **b.** Patient has achieved a ≥ 20% reduction in blood phenylalanine concentration from pre-treatment baseline (i.e., blood phenylalanine concentration before starting sapropterin therapy); OR
       - **c.** According to the prescriber, treatment with sapropterin has resulted in an increase in dietary phenylalanine tolerance; AND
     - **ii.** Patient is not receiving concomitant Palynziq (pegvaliase-pqpz subcutaneous injection) at a stable maintenance dose.
       Note: Concomitant use with Palynziq is permitted during Palynziq dose titration.

Employer Plans:

Product	Criteria
Kuvan (sapropterin	The patient has tried the bioequivalent generic products **sapropterin dihydrochloride tablets OR Javygtor tablets,** AND cannot take due to a formulation difference in the inactive

Product	Criteria
dihydrochloride Tablets)	ingredient(s) [for example, difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction **[documentation required]**.
Kuvan (sapropterin dihydrochloride) Powder for Oral Solution	The patient has tried the bioequivalent generic product, **sapropterin dihydrochloride powder for oral solution OR Javygtor powder for oral solution**, AND cannot take due to a formulation difference in the inactive ingredient(s) [for example, difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction **[documentation required]**.

Individual and Family Plans:

Product	Criteria
Javygtor (sapropterin dihydrochloride) Tablets	The patient has tried the bioequivalent generic product, **sapropterin dihydrochloride tablets**, AND cannot take due to a formulation difference in the inactive ingredient(s) [for example, difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction **[documentation required].**
Javygtor (sapropterin dihydrochloride) Powder for oral solution	The patient has tried the bioequivalent generic product, **sapropterin dihydrochloride powder for oral solution**, AND cannot take due to a formulation difference in the inactive ingredient(s) [for example, difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction **[documentation required]**.
Kuvan (sapropterin dihydrochloride) Tablets	The patient has tried the bioequivalent generic product, **sapropterin dihydrochloride tablets**, AND cannot take due to a formulation difference in the inactive ingredient(s) [for example, difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction **[documentation required]**.
Kuvan (sapropterin dihydrochloride) Powder for Oral Solution	The patient has tried the bioequivalent generic product, **sapropterin dihydrochloride powder for oral solution**, AND cannot take due to a formulation difference in the inactive ingredient(s) [for example, difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction **[documentation required]**.

Conditions Not Covered

Sapropterin products for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Concurrent Use with Sephience.** Sephience (sepiapterin) is a precursor to tetrahydrobiopterin (BH_4), a phenylalanine hydroxylase activator, indicated for the treatment of hyperphenylalaninemia (HPA) in adult and pediatric patients 1 month of age and older with sepiapterin-responsive phenylketonuria (PKU). There are no data available regarding combination use of sapropterin and Sephience.

References

1. Kuvan™ tablets and powder for oral solution [prescribing information]. Novato, CA: BioMarin; August 2024.
2. Levy H, Burton B, Cederbaum S, Scriver C. Recommendations for evaluation of responsiveness to tetrahydrobiopterin (BH(4)) in phenylketonuria and its use in treatment. *Mol Genet Metab*. 2007 Dec;92(4):287-291.
3. van Spronsen FJ, Blau N, Harding C, et al. Phenylketonuria. *Nat Rev Dis Primers*. 2021;7(1):36.
4. Hillert A, Anikster Y, Belanger-Quintana A, et al. The genetic landscape and epidemiology of phenylketonuria. *Am J Hum Genet*. 2020;107:234-250.
5. 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). *Genet Med*. 2025 Jan;27(1):101289.
6. van Wegberg AMJ, MacDonald A, Ahring K, et al. European guidelines on diagnosis and treatment of phenylketonuria: First revision. *Mol Genet Metab*. 2025;145:109125.

Revision Details

Type of Revision	Summary of Changes	Date
Selected Revision	**Phenylketonuria:** **Removed** criterion "No concomitant use with Palynziq once stabilized on Kuvan." **Reauthorization Criteria:** **Added** criterion "Patient has had a clinical response (e.g., cognitive and/or behavioral improvements) as determined by the prescriber." **Updated** criterion **from** "Treatment with sapropterin has resulted in an increase in dietary phenylalanine tolerance or an improvement in neuropsychiatric symptoms (e.g., cognitive and/or behavioral improvements)" **to** "Treatment with sapropterin has resulted in an increase in dietary phenylalanine tolerance, according to the prescriber." **Updated** criterion **from** "NOT receiving concomitant therapy with Palynziq (pegvaliase-pqpz)" **to** "Patient is not receiving concomitant	12/15/2024

	Palynziq (pegvaliase-pqpz subcutaneous injection) at a stable maintenance dose." **Preferred Product Table:** **Added** preferred product step requirement for Kuvan Tablets and Powder for Oral Solution and Javygtor Tablets and Powder for Oral Solution for Individual and Family Plans.	
Annual Revision	**Policy Title.** **Updated** from "Sapropterin" **to** "Phenylketonuria – Sapropterin" **Added** documentation required statement **Phenylketonuria** **Updated** authorization approval from 12 months **to** 12 weeks **Removed** "Diagnosis of phenylketonuria (PKU) confirmed by documentation of ONE of the following: Plasma phenylalanine concentration persistently above 120 µmol/L (2 mg/dL) and altered ratio of phenylalanine to tyrosine in the untreated state with normal BH4 cofactor metabolism. Finding of biallelic pathogenic or likely pathogenic variants in the PAH gene." **Updated** "Patient has had a clinical response (e.g., cognitive and/or behavioral improvements) as determined by the prescriber" **to** "According to the prescriber, patient has had a clinical response; OR Note: Examples of clinical response may include cognitive and/or behavioral improvements" **Updated** "NOT receiving concomitant therapy with Palynziq (pegvaliase-pqpz subcutaneous injection) at a stable maintenance dose" **to** "Patient is not receiving concomitant Palynziq (pegvaliase-pqpz subcutaneous injection) at a stable maintenance dose. Note: Concomitant use with Palynziq is permitted during Palynziq dose titration." **Employer Plans and Individual and Family Plans Preferred Product Table:** **Added [documentation required]** to criteria **Conditions Not Covered** **Added** Concurrent Use with Sephience	11/01/2025

The policy effective date is in force until updated or retired.