Effective Date.....12/15/2024
Coverage Policy Number.....IP0295

Sapropterin

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Related Coverage Resources

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 and have discretion in making individual coverage determinations. 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

This policy supports medical necessity review for the following sapropterin products:

- **Javygtor**™ (sapropterin dihydrochloride tablets and powder for oral solution)
- **Kuvan**™ (sapropterin dihydrochloride tablets and powder for oral solution)
- **sapropterin dihydrochloride** tablets and powder for oral solution

Medical Necessity Criteria

Sapropterin products (Javygtor, Kuvan, or sapropterin dihydrochloride) are considered medically necessary when the following are met:

1. **Phenylketonuria (PKU).** Individual meets **ALL** of the following criteria (A, B, C, D and E):
   A. Diagnosis of phenylketonuria (PKU) confirmed by documentation of **ONE** of the following:

i. 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
ii. Finding of biallelic pathogenic or likely pathogenic variants in the *PAH* gene

B. Sapropterin is prescribed in conjunction with a phenylalanine restricted diet
C. Medication is prescribed by, or in consultation with, a metabolic disease specialist (or specialist who focuses on the treatment of metabolic diseases)
D. Preferred product criteria is met for the products as listed in the below tables

Employer Plans:

Product	Criteria
Kuvan (sapropterin dihydrochloride Tablets)	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 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.
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.

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
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.
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.
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

Product	Criteria
	bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Reauthorization Criteria

Continuation of Sapropterin products (Javygtor, Kuvan, or sapropterin dihydrochloride) are considered medically necessary for phenylketonuria (PKU) when the above medical necessity criteria are met AND there is documentation of **BOTH** of the following:

1. **ONE** of the following:
    A. Patient has had a clinical response (e.g., cognitive and/or behavioral improvements) as determined by the prescriber
    B. Blood phenylalanine levels are being maintained within an acceptable range (120-600 µmol/L)
    C. The individual has achieved a greater than or equal to 20% reduction in blood phenylalanine concentration from pre-treatment baseline
    D. Treatment with sapropterin has resulted in an increase in dietary phenylalanine tolerance according to the prescriber
2. NOT receiving concomitant therapy with Palynziq (pegvaliase-pqpz subcutaneous injection) at a stable maintenance dose.

Authorization Duration

Initial approval duration is up to 12 months
Reauthorization approval duration is up to 12 months

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven (criteria will be updated as new published data are available).

Background

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.

Guidelines
According to the European guidelines for PKU (2017), there is consensus in the literature that patients with blood phenylalanine concentration > 600 micromol/L should be treated.[8] There is also consensus that patients with blood phenylalanine concentration < 360 micromol/L can remain untreated, but should be monitored. Patients with blood phenylalanine concentration between 360 to 600 micromol/L should be treated until 12 years of age. Treatment for life is recommended for any patient with PKU; however, it is also noted that patients ≥ 12 years of age with blood phenylalanine concentration < 600 micromol/L do not require treatment. All adults with PKU should have lifelong systematic follow-ups in specialized metabolic centers, due to specific risks which may occur during adulthood. With regards to target phenylalanine levels, in treated PKU patients up to 12 years of age, the target levels should be 120 to 360 micromol/L; in treated PKU patients ≥ 12 years of age, the target levels should be 120 to 600 micromol/L.

The American College of Medical Genetics and Genomics (ACMG) published practice guidelines (2014) for the diagnosis and management of phenylalanine hydroxylase (PAH) deficiency.[9] The guidelines recommend initiating treatment as early as possible, preferably within the first week of life with a goal of having blood phenylalanine levels in the treatment range within the first 2 weeks. Dietary restriction of phenylalanine intake is the mainstay of therapy for PKU. Blood phenylalanine levels in all patients should be maintained in the range of 120 to 360 micromol/L. The guidelines state that approximately 25% to 50% of patients with PAH deficiency are responsive to sapropterin. A significant decline in blood phenylalanine level is expected in responders once treatment is initiated (with phenylalanine-restricted diet); however, patients in the lower end of the treatment range (≤ 180 micromol/L) rarely show a decrease in blood phenylalanine level even if they are responsive to sapropterin. In these patients, responsiveness is determined by adding phenylalanine to the diet in a stepwise method. An improvement in neuropsychiatric symptoms or increase in phenylalanine tolerance without a decrease in blood phenylalanine levels is sufficient reasoning to continue therapy. According to the guidelines, there is strong evidence to support life-long treatment and maintenance of metabolic control in patients with PAH deficiency.

References

1. Kuvan™ tablets and powder for oral solution [prescribing information]. Novato, CA: BioMarin; February 2021.
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3. Blau N, van Spronsen FJ, Levy HL. Phenylketonuria. *Lancet*. 2010;376:1417-1427.
4. Feillet F, van Spronsen FJ, MacDonald A, et al. Challenges and pitfalls in the management of phenylketonuria. *Pediatrics*. 2010;126(2):333-341.
5. Levy HL, Milanowski A, Chakrapani A, et al for the Sapropterin Research Group. 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;370:504-510.
6. Burton BK, Bausell H, Katz R, et al. Sapropterin therapy increases stability of blood phenylalanine levels in patients with BH4-responsive phenylketonuria (PKU). *Mol Genet Metab*. 2010;101(2-3):110-114.
7. Burton BK, Nowacka M, Hennermann JB, et al. Safety of extended treatment with sapropterin dihydrochloride in patients with phenylketonuria: results of a phase 3b study. *Mol Genet Metab*. 2011;103(4):315-322.
8. van Wegberg AMJ, MacDonald A, Ahring A, et al. The complete European guidelines on phenylketonuria: diagnosis and treatment. *Orphanet J Rare Dis.* 2017;12:162.
9. Vockley J, Andersson HC, Antshel KM, et al. Phenylalanine hydroxylase deficiency: diagnosis and management guideline. Available at: https://www.acmg.net/docs/Phenylalanine_Hydrosylase_Deficiency_Practice_Guideline_AOP_Jan_2013.pdf . Accessed on August 23, 2024.

Revision Details

Type of Revision	Summary of Changes	Date
Selected Revision	**Phenylketonuria:**	12/15/2024

	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 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.	

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