PHARMACY COVERAGE GUIDELINE

JAVYGTOR™ (sapropterin dihydrochloride) oral
KUVAN® (sapropterin dihydrochloride) oral
PALYNZIQ™ (pegvaliase-pqpz) subcutaneous
Sapropterin Dihydrochloride oral
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

JAVYGTOR™ (sapropterin dihydrochloride) oral
KUVAN® (sapropterin dihydrochloride) oral
Sapropterin dihydrochloride oral

- **Criteria for initial therapy:** Kuvan (sapropterin dihydrochloride), Javygtor (sapropterin dihydrochloride), or sapropterin dihydrochloride are considered ***medically necessary*** and will be approved when **ALL** of the

following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a specialist with knowledge and expertise in metabolic diseases or genetic diseases

2. Individual is 1 month of age or older

3. Individual has a confirmed diagnosis of hyperphenylalaninemia (HPA) due to tetrahydrobiopterin (BH4) responsive phenylketonuria (PKU)

4. Individual is on a phenylalanine (PHE)-restricted diet

5. Individual has a phenylalanine (PHE) level above the recommended level for the individual's age or condition (baseline value must be submitted with the request)

6. Request for **brand** Kuvan (sapropterin dihydrochloride) and **brand** Javygtor (sapropterin dihydrochloride): Individual has failure, contraindication per FDA label, intolerance, or is not a candidate for **generic sapropterin dihydrochloride**

7. Kuvan (sapropterin dihydrochloride), Javygtor (sapropterin dihydrochloride), or sapropterin dihydrochloride will not be used concurrently with Palynziq (pegvaliase-pqpz)

Initial approval duration: 3 months

- **Criteria for continuation of coverage (renewal request):** Kuvan (sapropterin dihydrochloride), Javygtor (sapropterin dihydrochloride), or generic sapropterin dihydrochloride are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a specialist with knowledge and expertise in metabolic diseases or genetic diseases

2. PHE-restricted diet was not changed in any way during the initial trial of therapy with sapropterin dihydrochloride in order to determine responsiveness

3. Individual's condition has responded while on therapy with response defined as baseline PHE level and the most recent PHE level show at least a 20% decrease in PHE while on sapropterin dihydrochloride (levels must be submitted when requesting continued treatment

4. Individual has been adherent with the medication and a phenylalanine (PHE)-restricted diet

5. Request for continuation of **brand** Kuvan (sapropterin dihydrochloride) and **brand** Javygtor (sapropterin dihydrochloride): Individual has failure, contraindication per FDA label, intolerance, or is not a candidate for **generic sapropterin dihydrochloride**

6. Kuvan (sapropterin dihydrochloride), Javygtor (sapropterin dihydrochloride), or sapropterin dihydrochloride will not be used concurrently with Palynziq (pegvaliase-pqpz)

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

PALYNZIQ™ (pegvaliase-pqpz) subcutaneous

- **Criteria for initial therapy:** Palynziq (pegvaliase-pqpz) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a specialist with knowledge and expertise in metabolic diseases or genetic diseases

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of phenylketonuria (PKU)

4. Individual has received and completed a baseline **blood phenylalanine (PHE) level greater than 600 micromol/L (10 mg/dL) on existing PKU management** with continued monitoring of the individual as clinically appropriate

5. Individual is on a phenylalanine (PHE)-restricted diet

6. Individual has a current prescription for epinephrine

7. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for sapropterin dihydrochloride (Kuvan, Javygtor, or sapropterin dihydrochloride)

8. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

9. Individual will not be receiving Palynziq in combination with sapropterin dihydrochloride (Kuvan, Javygtor, or sapropterin dihydrochloride)

Initial approval duration: 9 months

- **Criteria for continuation of coverage (renewal request):** Palynziq (pegvaliase-pqpz) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a specialist with knowledge and expertise in metabolic diseases or genetic diseases

2. Individual has **ONE** of the following:
    a. Individual is on the maintenance dose and **ONE** of the following:
        i. There is documentation of at least a 20% decrease in PHE level from baseline (levels must be submitted when requesting continued treatment)
        ii. Blood PHE concentration is less than or equal to 600 micromol/L (10 mg/dL)
    b. Individual has not achieved an adequate clinical response to titration treatment and **ONE** of the following: (see Definitions section)
        i. Has not been titrated to the maximum allowed dose of 60 mg once daily
        ii. Has received less than 16 weeks of continuous treatment at the maximum allowed dose of 60 mg once daily

3. Individual has been adherent with the medication

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual is on a phenylalanine (PHE)-restricted diet

6. Individual has a current prescription for epinephrine

7. Individual will not be receiving Palynziq in combination with sapropterin dihydrochloride (Kuvan, Javygtor, or sapropterin dihydrochloride)

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

JAVYGTOR™ (sapropterin dihydrochloride) oral
KUVAN® (sapropterin dihydrochloride) oral
PALYNZIQ™ (pegvaliase-pqpz) subcutaneous
Sapropterin Dihydrochloride oral
Generic Equivalent (if available)

2. **Off-Label Use of Cancer Medications**

Description:

Sapropterin dihydrochloride (brand Kuvan, brand Javygtor, or generic) is an orally administered phenylalanine (PHE) hydroxylase activator approved to reduce blood PHE levels in patients one month of age or older with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin (BH4)-responsive phenylketonuria (PKU). Sapropterin is to be used with a phenylalanine restricted diet. Left untreated the condition can lead to profound neurocognitive and developmental defects. Neurologic damage can include severe mental retardation, microcephaly, delayed speech, seizures, and behavioral abnormalities. Conversely, prolonged low levels of blood PHE have been associated with catabolism and protein breakdown.

Palynziq (pegvaliase-pqpz) injection, for subcutaneous use is indicated to reduce blood phenylalanine concentrations in adult patients with PKU who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management. Palynziq should be discontinued in patients who have not achieved an adequate response after 16 weeks of continuous treatment with the maximum dosage of 60 mg once daily.

Because of the risk of anaphylaxis, Palynziq is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Palynziq REMS. All patients prescribed Palynziq must have a prescription for auto-injectable epinephrine. Patients should be instructed to carry the auto-injectable epinephrine with them at all times.

The underlying defect in PKU is a deficiency or a decrease in activity of the hepatic enzyme phenylalanine hydroxylase (PAH). PAH deficiency is an autosomal-recessive disorder. The gene is located on chromosome 12. More than 500 different mutations in the PAH gene have been described.

Sapropterin dihydrochloride is a biologically active synthetic form of naturally occurring BH4. It reduces blood PHE levels in patients with HPA by improving the normal metabolism of PHE. BH4 is a cofactor for the enzyme phenylalanine hydroxylase (PAH) that hydroxylates PHE through an oxidative reaction to form tyrosine (TYR). PAH activity is absent or deficient among patients with PKU. While these individuals are not deficient in endogenous BH4, some patients with PAH deficiency, who have some residual enzyme activity respond to administration of sapropterin dihydrochloride with an increase in the metabolism of PHE to TYR.

The mechanism by which residual PAH activity is enhanced is unclear, but BH4 may act as a pharmacologic chaperone leading to improved folding and increased stability of the mutant protein. In clinical trials, approximately 20–75% of the patients with PAH deficiency are BH4-responsive. Patients whose blood PHE does not decrease after 1 month of treatment at 20 mg/kg per day are considered non-responders and treatment with sapropterin dihydrochloride should be discontinued in these patients. Current literature cites a 30% reduction in PHE levels as evidence for responsiveness to sapropterin dihydrochloride.

Sapropterin dihydrochloride must be used in conjunction with a PHE restricted diet. Active management of dietary PHE intake is the mainstay of therapy and requires restriction of dietary PHE intake necessitating a decrease in the intake of natural protein and replacing it with a protein (amino acid mixture) source devoid of PHE. A provider

experienced in metabolic disorders and a nutritionist team-based approach should manage this therapy. Dietary manipulation will be required to maintain appropriate blood PHE levels with frequent dietary modification to respond to growth, life stages, concurrent illness, and comorbidities.

Pegvaliase-pqpz is a phenylalanine-metabolizing enzyme composed of recombinant phenylalanine ammonia lyase (rAvPAL) conjugated to N-hydroxysuccinimide (NHS)-methoxypolyethylene glycol (PEG). Pegvaliase-pqpz converts phenylalanine to ammonia and trans-cinnamic acid. Trans-cinnamic acid and its final product, benzoic acid, are conjugated with glycine and excreted in the urine. Pegvaliase-pqpz substitutes for the deficient phenylalanine hydroxylase (PAH) enzyme activity in patients with PKU and reduces blood phenylalanine concentrations. The metabolism of phenylalanine ammonia lyase is expected to occur via catabolic pathways and be degraded into small peptides and amino acids.

The American College of Medical Genetics and Genomics 2014 practice guideline suggests blood PHE levels should be maintained in the range of 120–360 µmol/L for all patients, although there is no evidence to suggest normalization of PHE levels is required and lower levels of 60-120 µmol/L should not be viewed as too low. It should be noted that measurement of PHE levels in blood varies and is dependent on the analytical method used; requiring consistency in testing methodology in order to interpret the resultant values.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Palynziq dosing:

Treatment phase	Palynziq dosage	Duration*
Induction	2.5 mg once weekly	4 weeks
Titration	2.5 mg twice weekly	1 week
	10 mg once weekly	1 week
	10 mg twice weekly	1 week
	10 mg four times per week	1 week
	10 mg once daily	1 week
Maintenance†	20 mg once daily	24 weeks
	40 mg once daily	16 week
Maximum¶	60 mg once daily	16 weeks

* Additional time may be required prior to each dosage escalation based on patient tolerability.
† Individualize treatment to the lowest effective and tolerated dosage. Consider increasing to 40 mg once daily in patients who have not achieved a response with 20 mg once daily continuous treatment for at least 24 weeks. Consider increasing to a maximum of 60 mg once daily in patients who have not achieved a response with 40 mg once daily continuous treatment for at least 16 weeks.
¶ Discontinue Palynziq in patients who have not achieved an adequate response after 16 weeks of continuous treatment at the maximum dosage of 60 mg once daily.

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Resources:

Kuvan (sapropterin) tab & oral powder product information, revised by BioMarin Pharmaceutical, Inc. 08-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 25, 2024.

Javygtor (sapropterin) tab & oral powder product information, revised by Dr. Reddys Laboratories, Inc. 01-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 25, 2024.

Sapropterin tab & oral powder product information, revised by Dr. Reddys Laboratories, Inc. Inc. 12-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 25, 2024.

Palynziq (pegvaliase-pqpz) subcutaneous injection product information, revised by BioMarin Pharmaceutical, Inc. 11-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 25, 2024.

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Longo N, Dimmock D, Levy H, et al.: Evidence- and consensus-based recommendations for the use of pegvaliase in adults with phenylketonuria. Genetics in Medicine 2019 Aug; 21 (8):1851-1867. Accessed on November 10, 2022. Re-evaluated January 06, 2025.

Vockley J, Andersson HC, Antshel KM, et al.: Phenylalanine hydroxylase deficiency: diagnosis and management guideline. Genetics in Medicine 2014 Feb; 16 (2): 188-200. doi:10.1038/gim.2013.157. Accessed November 01,2018. Re-evaluated January 06, 2025.

Van Wegberg AMJ, MacDonald A, Ahring K, et al.: The complete European guidelines on phenylketonuria: diagnosis and treatment. Orphanet J Rare Diseases 2017;12:162. DOI 10.1186/s13023-017-0685-2. Accessed January 28, 2021. Re-evaluated January 06, 2025.

Regier DS, Greene CL. Phenylalanine hydrolase deficiency. 2000 Jan 10 [Updated 2017 Jan 5]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available at: https://www.ncbi.nlm.nih.gov/books/. Accessed January 25, 2023. Re-evaluated January 06, 2025.