LOUISIANA BLUE

Phenylalanine Hydroxylase Activators

Policy # 00303
Original Effective Date: 08/17/2011
Current Effective Date: 01/01/2026

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: pegvaliase-pqpz (Palynziq™)‡ is addressed separately in medical policy 00644.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

sapropterin dihydrochloride

Based on review of available data, the Company may consider the use of sapropterin dihydrochloride (Kuvan®, Javygtor™, Zelvysia™, generics)‡ for the treatment of hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4-) responsive phenylketonuria (PKU) to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for the use of sapropterin dihydrochloride (Kuvan, Javygtor, Zelvysia, generics) for the treatment of HPA will be considered when the following criteria are met:

- Patient has a diagnosis of HPA due to BH4- PKU; AND
- Patient is on a phenylalanine (Phe) restricted diet; AND
- Patient is NOT using the requested drug in combination with pegvaliase-pqpz (Palynziq™)‡ or sepiapterin (Sephience®)‡; AND
- If the request is for brand Kuvan, patient has tried and failed (e.g., intolerance or inadequate response) GENERIC sapropterin dihydrochloride (e.g., Javygtor, Zelvysia, generics) unless there is clinical evidence or patient history that suggests GENERIC sapropterin dihydrochloride (e.g., Javygtor, Zelvysia, generics) will be ineffective or cause an adverse reaction to the patient.
  *(Note: this specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of brand Kuvan when the patient has NOT tried and failed GENERIC sapropterin dihydrochloride (e.g., Javygtor, Zelvysia, generics) to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of sapropterin dihydrochloride (Kuvan, Javygtor, Zelvysia, generics) when patient selection criteria are not met (except the criterion denoted above as **not medically necessary****) to be **investigational.***

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

sepiapterin (Sephience)

Based on review of available data, the Company may consider the use of sepiapterin (Sephience) for the treatment of hyperphenylalaninemia (HPA) due to sepiapterin-responsive phenylketonuria (PKU) to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for the use of sepiapterin (Sephience) for the treatment of HPA will be considered when the following criteria are met:

Initial (3 months)

- Patient has a diagnosis of hyperphenylalaninemia (HPA) due to phenylketonuria **(**PKU); AND
- Patient is ≥ 1 month of age; AND
- Patient is on a phenylalanine restricted diet and will continue during treatment with Sephience; AND
- Patient is NOT using the requested drug in combination with sapropterin products (Kuvan, generics) or pegvaliase-pqpz (Palynziq); AND
- Documentation is provided that the patient's blood phenylalanine concentration is currently ≥ 360 micromol/L on existing management (e.g., dietary restrictions, treatment with sapropterin [Kuvan, generics] or Palynziq); AND
  *(Note: this specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- Patient meets ONE of the following:
  - Patient has tried and failed (e.g., intolerance or inadequate response) GENERIC sapropterin dihydrochloride (e.g., Javygtor, Zelvysia, generics) unless there is clinical evidence or patient history that suggests GENERIC sapropterin dihydrochloride (e.g., Javygtor, Zelvysia, generics) will be ineffective or cause an adverse reaction to the patient; OR

- Prescriber attests that the patient is known to have complete phenylalanine hydroxylase (PAH) deficiency, consistent with classic PKU. See Policy Background section.

*(Note: this specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*

Continuation

- Patient has received an initial authorization for Sephience; AND
- Patient has experienced a positive clinical response to therapy, as evidenced by documentation of a recent blood phenylalanine level ≥ 20% lower than baseline, OR blood phenylalanine levels are being maintained in an acceptable range (less than 360 micromol/L); AND

  *(Note: this specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- Patient is NOT using the requested drug in combination with sapropterin products (Kuvan, generics) or pegvaliase-pqpz (Palynziq); AND
- Patient is on a phenylalanine restricted diet and will continue during treatment with Sephience.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of sepiapterin (Sephience) when the patient has NOT tried and failed GENERIC sapropterin dihydrochloride (e.g., Javygtor, Zelvysia, generics) OR is NOT known to have complete phenylalanine hydroxylase (PAH) deficiency, consistent with classic PKU, to be **not medically necessary.****

Based on review of available data, the Company considers the use of sepiapterin (Sephience) when the patient's phenylalanine concentration is currently < 360 micromol/L on existing management to be **not medically necessary.****

Based on review of available data, the Company considers the continued use of sepiapterin (Sephience) when the patient has NOT experienced a positive clinical response to therapy to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of sepiapterin (Sephience) when patient selection criteria are not met (except the criteria denoted above as **not medically necessary****) to be **investigational.***

Background/Overview

Sapropterin dihydrochloride is a synthetic preparation of naturally occurring BH4-, which is a cofactor for the enzyme phenylalanine hydroxylase (PAH). PAH hydroxylates Phe through an oxidative reaction to form tyrosine. In patients with PKU, PAH activity is deficient or absent. Treatment with BH4- can activate residual PAH enzyme, improve the normal oxidative metabolism of Phe, and decrease Phe levels in some patients. In patients with PKU who are responsive to treatment, blood Phe levels decrease within 24 hours after administration of sapropterin, although maximal effect on Phe levels may take up to one month. In 8-day and 6-week pivotal trials, response to sapropterin dihydrochloride treatment was defined as ≥ 30% decrease in blood Phe concentration from baseline. However, in some cases (e.g., patients with mild HPA, neonates or children < 4 years of age, or pregnant women), a 20% reduction in blood Phe concentration may be sufficient. Kuvan is the brand name of sapropterin dihydrochloride, and Javygtor and Zelvysia are the trademarked names of sapropterin dihydrochloride, although they are still generic products. Sapropterin dihydrochloride is supplied as brand and generic 100 mg tablets. Both the brand and generic are also available in unit dosed powder packets for oral solution containing either 100 mg or 500 mg of the drug. The recommended starting dose of sapropterin is 10mg/kg/day taken once daily. Doses of sapropterin may be adjusted in the range of 5-20 mg/kg taken once daily. Doses of sapropterin above 20 mg/kg/day have not been evaluated.

Sephience represents the third pharmacological treatment option available for PKU, in addition to sapropterin and Palynziq. Like sapropterin, sepiapterin functions to activate residual phenylalanine hydroxylase through BH_4; however, it is a precursor of BH_4 while sapropterin is a synthetic form of the cofactor. Sephience is available as an oral powder in 250 mg and 1,000 mg unit-dose packets and should be dosed once daily with food. Biochemical response to Sephience treatment cannot generally be pre-determined by laboratory testing (e.g., molecular testing), and should be determined through a therapeutic evaluation of Sephience. According to the prescribing information, baseline blood Phe concentration should be assessed prior to therapy and again within 2 weeks of initiating Sephience to evaluate for responsiveness. The recommended starting dose of Sephience is based on the patient's age and weight; the FDA approved dosage and administration recommendations may be found within Sephience's prescribing information. For patients < 2 years of age, the dose should be titrated incrementally if blood Phe levels do not decrease. Blood Phe levels should be monitored while on therapy and the daily dosage modified within the range of 7.5 mg/kg to 60 mg/kg per day. Sephience should be discontinued if the blood Phe level does not decrease after 2 weeks of treatment at the maximum daily dosage of 60 mg/kg.

All patients with PKU who are treated with phenylalanine hydroxylase inhibitors should be on a dietary protein and Phe-restricted diet that is based on blood Phe levels, according to the prescribing information for both sapropterin and sepiapterin.

Phenylketonuria

PKU is an autosomal recessive disorder caused by a defect in the gene encoding the hepatic enzyme, PAH, which is responsible for hydroxylating Phe through an oxidative reaction to form tyrosine. In patients with PKU, PAH activity is deficient or absent causing elevated blood Phe levels and

decreased tyrosine levels. Complete enzyme deficiency results in classic PKU, in which serum phenylalanine plasma concentrations in an untreated, newly diagnosed newborn infant exceed 20 mg/dL (1200 micromol/L). Residual enzyme activity causes moderate PKU (Phe concentrations 900 to 1200 micromol/L), mild PKU (Phe concentrations 600 to 900 micromol/L), mild hyperphenylalaninemia (HPA; Phe concentrations 360 to 600 micromol/L), and benign mild HPA that typically does not require treatment (Phe concentrations 120 to 360 micromol/L). Tetrahydrobiopterin (BH4-) is an essential cofactor required for the activity of multiple enzymes, including PAH. The lack of BH4- could result in PKU from HPA. Elevated levels of phenylalanine can lead to severe brain damage, behavioral abnormalities, mental retardation, speech impediments, etc. Sapropterin dihydrochloride and sepiapterin work in the body to supplement BH4-, which in turn helps to convert Phe via PAH appropriately and therefore lowers the levels of Phe in the blood. The 2023 American College of Medical Genetics and Genomics (ACMG) Clinical Guidelines recommend treating individuals with blood Phe levels greater than 360 micromol/L and maintaining Phe levels to < 360 micromol/L for life as it is associated with higher IQ levels and better intellectual outcomes.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

In December 2007, the U.S. FDA granted marketing approval for Kuvan (sapropterin dihydrochloride) tablets, the first specific drug therapy approved to reduce blood Phe levels in patients with HPA due to BH4-responsive PKU in adult and pediatric patients one month of age and older. In September of 2022, Javygtor, a trademarked generic formulation of sapropterin dihydrochloride was approved. A second trademarked generic formulation, Zelvysia, received approval in April of 2025.

In July of 2025, Sephience was approved for the treatment of hyperphenylalaninemia in adult and pediatric patients 1 month of age and older with sepiapterin-responsive PKU. Sephience is to be used in conjunction with a phenylalanine (Phe)- restricted diet.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

Kuvan

Kuvan was studied in four clinical trials. Study 1 was a multicenter, open-label, uncontrolled clinical trial of 489 patients with PKU, ages 8 to 48 years (mean 22 years), who had baseline blood Phe levels ≥ 450 µmol/L and who were not on Phe-restricted diets. All patients received treatment with

Kuvan 10 mg/kg/day for 8 days. For the purposes of this study, response to Kuvan treatment was defined as a ≥30% decrease in blood Phe from baseline. At Day 8, 96 patients (20%) were identified as responders.

Study 2 was a multicenter, double-blind, placebo-controlled study of 88 patients with PKU who responded to Kuvan in Study 1. After a washout period from Study 1, patients were randomized equally to either Kuvan 10mg/kg/day (N = 41) or placebo (N = 47) for 6 weeks. Efficacy was assessed by the mean change in blood Phe level from baseline to Week 6 in the Kuvan-treated group as compared to the mean change in the placebo group. The results showed that at baseline, the mean standard deviation (±SD) blood Phe level was 843 (±300) µmol/L in the Kuvan-treated group and 888 (±323) µmol/L in the placebo group. At Week 6, the Kuvan-treated group had a mean (±SD) blood Phe level of 607 (±377) µmol/L, and the placebo group had a mean blood Phe level of 891 (±348) µmol/L. At Week 6, the Kuvan- and placebo-treated groups had mean changes in blood Phe level of –239 and 6 µmol/L, respectively (mean percent changes of –29% (± 32) and 3% (±33), respectively). The difference between the groups was statistically significant ($p < 0.001$).

Study 3 was a multicenter, open-label, extension study in which 80 patients who responded to Kuvan treatment in Study 1 and completed Study 2 underwent 6 weeks of forced dose-titration with 3 different doses of Kuvan. Treatments consisted of 3 consecutive 2-week courses of Kuvan at doses of 5, then 20, and then 10 mg/kg/day. Blood Phe level was monitored after 2 weeks of treatment at each dose level. At baseline, mean (±SD) blood Phe was 844 (±398) µmol/L. At the end of treatment with 5, 10, and 20 mg/kg/day, mean (±SD) blood Phe levels were 744 (±384) µmol/L, 640 (±382) µmol/L, and 581 (±399) µmol/L, respectively.

Study 4 was a multicenter study of 90 children with PKU, ages 4 to 12 years, who were on Phe-restricted diets and who had blood Phe levels ≤ 480µmol/L at screening. All patients were treated with open-label Kuvan 20 mg/kg/day for 8 days. Response to Kuvan was defined as a ≥ 30% decrease in blood Phe from baseline at Day 8. At Day 8, 50 patients (56%) had a ≥ 30% decrease in blood Phe.

Sephience

Trial 1

Trial 1 was a two-part trial in adult and pediatric patients who had a diagnosis of PKU with hyperphenylalaninemia with at least 2 blood Phe measurements ≥ 600 µmol/L. The mean age of the trial patients was 17 years (range: 1 to 61 years).

In Part 1, 157 patients received open-label treatment with Sephience: 7.5 mg/kg orally in patients 0 to < 6 months of age, 15 mg/kg in patients 6 to < 12 months of age, 30 mg/kg in patients 12 months to < 2 years of age, or 60 mg/kg in patients ≥ 2 years of age per day for 14 days. In Part 1, 66% of PKU patients showed a biochemical response to Sephience with a > 30% or greater reduction in Phe level.

In Part 2, after the 2-week washout period from Part 1, 98 patients aged 2 years and older who demonstrated a ≥ 30% reduction in blood Phe levels to Sephience treatment in Part 1 were randomized in a double-blind fashion to either Sephience 20 mg/kg daily for Weeks 1 and 2, 40 mg/kg daily for Weeks 3 and 4, 60 mg/kg daily for Weeks 5 and 6, or placebo for 6 weeks to assess efficacy. Twelve additional patients who had shown a 15% to 30% reduction in blood Phe during Part 1 were enrolled in Part 2 but were not included in the primary efficacy analysis. In Part 2, the primary efficacy was assessed in patients who demonstrated a ≥ 30% reduction in blood Phe levels during Part 1 (N = 98) by the mean change in blood Phe level from baseline to Weeks 5 and 6 in the Sephience-treated group as compared to the mean change in the placebo group. In Part 2, 55 patients in the Sephience group and 54 patients in the placebo group completed the treatment period. One patient in the Sephience group discontinued treatment. There was a significant reduction in blood Phe concentration of 62.8% after 6 weeks of Sephience versus 1.4% on placebo (treatment difference -64.2; 95% confidence interval: -74.1, -54.4).

Trial 2

Supportive efficacy data were provided from Trial 2, which is an ongoing, multicenter, open-label trial in adult and pediatric patients with a clinical diagnosis of PKU with hyperphenylalaninemia. At the data cutoff date, 169 patients, including 65 adult and 104 pediatric patients received treatment with Sephience. Five patients 2 to < 17 years of age and 65 patients ≥17 years of age received Sephience 60 mg/kg. Of the 9 patients under the age of 2 years, 6 patients (66%) had a ≥ 30% decrease in blood Phe from baseline at Weeks 1 and 2. The baseline Phe level in patients 2 years and under was 311.4 µmol/L and the mean absolute change in Phe from baseline to Weeks 1 and 2 in this age group was -125 µmol/L (standard deviation 265.9 µmol/L).

References

1. Kuvan [package insert]. Novato, CA: BioMarin Pharmaceuticals; March 2020.
2. Javygtor [package insert]. Princeton, NJ: Dr. Reddy's Laboratories Inc; January 2022.
3. Zelvysia [package insert]. Piscataway, NJ: Acucta Pharmaceuticals, Inc. April 2025.
4. Sephience [package insert]. Warren, NJ: PTC Therapeutics, Inc. July 2025.
5. Sephience Drug Evaluation. Express Scripts. August 2025.
6. Sephience New Drug Review. IPD Analytics. September 2025.
7. Muntau AC, et al. Effects of oral sepiapterin on blood Phe concentration in a broad range of patients with phenylketonuria (APHENITY): results of an international, Phase 3, randomized, double-blind, placebo-controlled trial. *Lancet*. 2024;404(10460):1333-1345.
8. Levy H, Burton B, et al. Recommendations for evaluation of responsiveness to tetrahydrobiopterin (BH4) in phenylketonuria and its use in treatment. *Mol Genet Metab*. 2007;92:287-291.
9. 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;27(1):101289.
10. Palynziq [package insert]. Biomarin Pharmaceutical Inc. Novato, California. November 2020.

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Policy History

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08/04/2011	Medical Policy Committee review
08/17/2011	Medical Policy Implementation Committee approval. New policy.
08/02/2012	Medical Policy Committee review
08/15/2012	Medical Policy Implementation Committee approval. No change to coverage.
02/19/2013	Coding updated
08/01/2013	Medical Policy Committee review
08/21/2013	Medical Policy Implementation Committee approval. Reworded the patient selection criteria, however there is no coverage change. Added background on phenylketonuria. Changed the rationale/source section to info from the package insert regarding the clinical trials.
08/07/2014	Medical Policy Committee review
08/20/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/06/2015	Medical Policy Committee review
08/19/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/04/2016	Medical Policy Committee review
08/17/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2017	Medical Policy Committee review
08/23/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/09/2018	Medical Policy Committee review
08/15/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/01/2019	Medical Policy Committee review
08/14/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/06/2020	Medical Policy Committee review
08/12/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/04/2021	Medical Policy Committee review
02/10/2021	Medical Policy Implementation Committee approval. Title changed to reflect availability of generics. Generic added to policy with new criterion requiring trial of generic prior to brand.
12/02/2021	Medical Policy Committee review
12/08/2021	Medical Policy Implementation Committee approval. Added criteria statement clarifying that Kuvan should not be used in combination with Palynziq.
12/01/2022	Medical Policy Committee review

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12/14/2022	Medical Policy Implementation Committee approval. Added Javygtor, which is generic sapropterin, to the policy. Updated background information.
12/07/2023	Medical Policy Committee review
12/13/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/05/2024	Medical Policy Committee review
12/11/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/04/2025	Medical Policy Committee review
12/10/2025	Medical Policy Implementation Committee approval. Added new product, Sephience, with relevant criteria. Added new generic product, Zelvysia, to the policy. Updated background information and rationale. Title changed from "sapropterin dihydrochloride (Kuvan, generics)" to "Phenylalanine Hydroxylase Activators".

Next Scheduled Review Date: 12/2026

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.