Clinical Policy: Sepiapterin (Sephience)

Reference Number: PA.CP.PHAR.708
Effective Date: 02/2026
Last Review Date: 04/2026

Description

Sepiapterin (Sephience™) is a phenylalanine hydroxylase (PAH) activator.

FDA Approved Indication(s)

Sephience is indicated for the treatment of hyperphenylalaninemia (HPA) in adult and pediatric patients 1 month of age and older with sepiapterin-responsive phenylketonuria (PKU). Sephience is to be used in conjunction with a phenylalanine (Phe)-restricted diet.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of PA Health & Wellness® that Sephience is **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 disease specialist, 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 Sephience;
5. Failure of generic sapropterin (Kuvan®) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
6. Sephience is not prescribed concurrently with sapropterin (Kuvan, Javygtor, Zelvysia) or Palynziq™, unless titrating with the plan to discontinue Sephience;
7. Documentation of member's current weight (in kg);
8. Dose does not exceed 60 mg/kg per day.

Approval duration: 6 months

B. Other diagnoses/indications

1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

II. Continued Therapy

A. Phenylketonuria (must meet all)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies;

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 Sephience;
4. Sephience is not prescribed concurrently with sapropterin (Kuvan, Javygtor, Zelvysia) or Palynziq, unless titrating with the plan to discontinue Sephience;
5. Documentation of member's current weight (in kg);
6. If request is for a dose increase, new dose does not exceed 60 mg/kg per day.

Approval duration: 12 months

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

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

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 – PA.CP.PMN.53

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
HPA: hyperphenylalaninemia
PKU: phenylketonuria
Phe: phenylalanine

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
sapropterin (Kuvan®, Javygtor, Zelvysia)	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

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings
None reported

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
PKU	**Age less than 6 months**: 7.5 mg/kg PO QD **Age 6 months to less than 1 year**: 15 mg/kg PO QD **Age 1 year to less than 2 years**: 30 mg/kg PO QD **Age ≥ 2 years**: 60 mg/kg PO QD For calculated daily doses less than 1,000 mg, prepare Sephience as a liquid mixture with a final concentration of 25 mg/mL. Round the dose *up* to the nearest 250 mg to determine the number of Sephience packets required. For calculated daily doses 1,000 mg or greater, round the dose to the nearest 250 mg to determine the number of Sephience packets required.	60 mg/kg/day

VI. Product Availability

Oral powder: 250 mg, 1,000 mg

VII. References

1. Sephience Prescribing Information. Warren, NJ: PTC Therapeutics, Inc.; July 2025. Available at: www.sephience.com. Accessed: March 5, 2026.
2. Muntau AC, Longo N, Ezgu F, 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, randomised, double-blind, placebo-controlled trial. Lancet. Oct 2024; 404(10460): 1333-1345.
3. 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): Article 101289. https://doi.org/10.1016/j.gim.2024.101289.
4. 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
Policy created	01/2026
2Q 2026 annual review: bringing forward to align with the annual review cycle for Kuvan and Palynziq; references reviewed and updated.	04/2026