MEDICAL MUTUAL®

Drug Policy

Policy:	Sephience (sepiapterin oral powder)	Annual Review Date: 04/16/2026 Last Revised Date: 04/16/2026

OVERVIEW

Sephience, a phenylalanine hydroxylase (PAH) activator, is indicated for the treatment of hyperphenylalaninemia (HPA) in adult and pediatric patients one month of age and older with sepiapterin-responsive **phenylketonuria (PKU).**[1]

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

POLICY STATEMENT

This policy involves the use of Sephience. Prior authorization is recommended for pharmacy benefit coverage of Sephience. Approval is recommended for those who meet the conditions of coverage in the **Criteria and Initial/Extended Approval** for the diagnosis provided. **Conditions Not Recommended for Approval** are listed following the recommended authorization criteria. Requests for uses not listed in this policy will be reviewed for evidence of efficacy and for medical necessity on a case-by-case basis.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Sephience as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Sephience be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is allowed, a response to therapy is required for continuation of therapy unless otherwise noted below.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Sephience is recommended in those who meet the following criteria:

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, iii, iv, v, and vi):
     - **i.** The patient is ≥ 1 month of age; AND
     - **ii.** The patient has a confirmed diagnosis of PKU, with recent blood Phe level prior to initiating treatment* ; AND
     - **iii.** The medication is prescribed in conjunction with a phenylalanine-restricted diet; AND
     - **iv.** The medication is prescribed by or in consultation with a metabolic disease specialist (or specialist who focuses on the treatment of metabolic diseases); AND

v. Patient has tried Kuvan or generic Sapropterin product with inadequate response, defined as blood Phe ≥ 360 µmol/L, despite consistent use in combination with dietary Phe restriction*; AND

vi. 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. OR

B) Patients is Currently Receiving Sephience. 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 Sephience should be considered under Initial Therapy.

i. Patient meets ONE of the following (a, b, c or d):

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 blood phenylalanine levels ≤ 360 micromol/L*; OR

c) Patient has achieved a ≥ 20% reduction in blood phenylalanine concentration from pre-treatment baseline* (i.e., blood phenylalanine concentration before starting Sephience therapy); OR

d) According to the prescriber, treatment with Sephience 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.

Initial Approval/ Extended Approval.
A) *Initial Approval: 12 weeks*
B) *Extended Approval: 1 year*

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Sephience has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

1. **Concurrent Use with Sapropterin (Kuvan, Javygtor, Zelvysia, generic).** Sapropterin is a synthetic form of tetrahydrobiopterin (BH_4), a phenylalanine hydroxylase activator, indicated for adult and pediatric patients one month of age and older with hyperphenylalaninemia due to BH_4-responsive phenylketonuria. There are no data available regarding combination use of sapropterin and Sephience.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

***Documentation Requirements:**

The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the drug provided or services performed were not medically necessary, investigational, or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

REFERENCES

1. Sephience™ oral powder [prescribing information]. Warren, NJ: PTC Therapeutics; July 2025.
2. van Spronsen FJ, Blau N, Harding C, et al. Phenylketonuria. *Nat Rev Dis Primers*. 2021;7(1):36.
3. Hillert A, Anikster Y, Belanger-Quintana A, et al. The genetic landscape and epidemiology of phenylketonuria. *Am J Hum Genet*. 2020;107:234-250.
4. 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;92:287-291.
5. 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*. 2024;404:133-45.
6. 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.