Drug Coverage Policy

Effective Date.....11/15/2025
Coverage Policy Number.....IP0764
Policy Title.....Sephience

Phenylketonuria – Sephience for Individual and Family Plans

- Sephience™ (sepiapterin oral powder - PTC Therapeutics)

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 where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. 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
Sephience, a phenylalanine hydroxylase (PAH) activator, is indicated for the treatment of hyperphenylalaninemia (HPA) in adult and pediatric patients 1 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.

Dose Titration
The recommended starting dosage of Sephience is based on the patient's age and is administered orally once daily (see Table 1).[1] The maximum daily dose for all patients is 60 mg/kg.

Table 1: Recommended Starting Dosage of Sephience in Pediatric and Adult Patients

Age	Sephience (mg/kg) per day
Less than 6 months	7.5 mg/kg
6 months to less than 1 year	15 mg/kg
1 year to less than 2 years	30 mg/kg
2 years and older	60 mg/kg

For patients less than 2 years of age, after initiating treatment at the starting dosage by age (Table 1), blood phenylalanine (Phe) levels should be checked to determine response to treatment within 2 weeks.[1] If blood Phe does not decrease, Sephience dosage may be titrated incrementally based on blood Phe levels to a maximum daily dosage of 60 mg/kg. If the patient's blood Phe does not decrease after 2 weeks of treatment at the maximum daily dosage of 60 mg/kg, Sephience should be discontinued for lack of biochemical response.

Disease Overview
Phenylketonuria (PKU) or phenylalanine hydroxylase (PAH) deficiency is an autosomal recessive disorder caused by pathogenic variants in the *PAH* gene.[2] PAH converts phenylalanine (Phe) to tyrosine and requires the co-substrate tetrahydrobiopterin (BH_4). With PAH deficiency, Phe can accumulate and lead to brain dysfunction resulting in severe intellectual disability, epilepsy, and behavioral problems. The incidence of PKU in the United States is approximately 1 in 25,000, which equates to approximately 13,600 individuals living with PKU.[3]

Sephience is a precursor of the enzymatic BH_4 which activates PAH. A reduction in blood Phe concentration of ≥ 30% is widely accepted as responsive; however, a lower degree of responsiveness (e.g., 20%) may be sufficient in some individual circumstances.[4]

Clinical Efficacy
The pivotal clinical trial (APHENITY) was divided into two parts.[5] During part one, patients received a fixed dose of Sephience based on their age for 2 weeks and were then assessed for responsiveness (defined as ≥ 15% reduction in blood Phe). Of the 156 patients assessed for responsiveness, 103 (66%) had a ≥ 30% decrease in blood Phe concentration and 11 (7%) had a ≥ 15% to < 30% decrease in blood Phe concentration. Patients ≥ 2 years old who were responsive entered a 2-week washout period and were then randomized to either Sephience or placebo. Only patients with a ≥ 30% decrease in blood Phe concentration were included in the primary analysis. The primary endpoint was mean change in blood Phe concentration from baseline to Week 6 in part two and was significantly lower in the Sephience group compared to placebo (-63% vs. +1%, respectively [$P < 0.0001$]).

Guidelines
Sephience is not addressed as an FDA-approved therapy in guidelines (mentioned as an investigational therapy).

In 2023, the American College of Medical Genetics and Genomics (ACMG) updated their practice guidelines for the diagnosis and management of phenylalanine hydroxylase (PAH) deficiency.[6] ACMG recommends 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 intelligence quotient (IQ) levels. ACMG advocates combination of therapies (e.g., dietary restriction, use of medical foods that are Phe-free or low in Phe, sapropterin, Palynziq) and individualization of treatment to improve blood Phe levels. Therapy resulting in a reduction of blood Phe, increase in dietary Phe tolerance, or improvement in clinical symptoms should be continued.

European guidelines (2025) are available for diagnosis and management of PKU.[7] The guidelines classify PKU as either not requiring treatment (Phe < 360 micromol/L), requiring treatment and co-factor (i.e., sapropterin) responsive, or requiring treatment and co-factor non-responsive. Early treatment is advocated (ideally before 10 days of age), and children < 12 years of age should aim for a Phe level of 120 to 360 micromol/L. However, unlike the US guidelines, the target level for children ≥ 12 to 18 years old and for adults > 18 years old is higher, at 120 to 600 micromol/L (except in pregnancy where the target level is 120 to 360 micromol/L).

Coverage Policy

Policy Statement
Prior Authorization is required for benefit coverage of Sephience. All approvals are provided for the duration noted below. 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 to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information.

Sephience is considered medically necessary when the following are met:

FDA-Approved Indication

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 BOTH of the following (i, ii and iii):
     - **i.** The medication is prescribed in conjunction with a phenylalanine-restricted diet; AND
     - **ii.** The medication is prescribed by or in consultation with a metabolic disease specialist (or specialist who focuses on the treatment of metabolic diseases); AND
     - **iii.** Preferred product criteria is met for the product(s) as listed in the below table(s) [Individual and Family Plans]; 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, or c):

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

Individual and Family Plans:

Product	Criteria
Sephience (sepiapterin oral powder)	Patient meets ONE of the following (1 or 2): 1. Patient has tried and, according to the prescriber, has experienced inadequate efficacy OR significant intolerance with a sapropterin tablet or powder packet **[documentation required]** 2. Approve if the patient has already been started on Sephience and is determined to be a responder, according to the prescriber.

Conditions Not Covered

Sephience for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

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 (HPA) due to BH_4-responsive phenylketonuria. There are no data available regarding combination use of sapropterin and Sephience.

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.
7. van Wegberg AMJ, MacDonald A, Ahring K, et al. European guidelines on diagnosis and treatment of phenylketonuria: First revision. *Mol Genet Metab*. 2025;145:109125.

Revision Details

Type of Revision	Summary of Changes	Date
New	New policy.	11/15/2025

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