VENTURA COUNTY
HEALTH CARE PLAN

PRIOR AUTHORIZATION POLICY

POLICY: Phenylketonuria – Sephience Prior Authorization Policy
- Sephience™ (sepiapterin oral powder – PTC Therapeutics)

REVIEW DATE: 07/30/2025; selected revision 10/29/2025

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.

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

PKU or phenylalanine hydroxylase (PAH) deficiency is an autosomal recessive disorder caused by pathogenic variants in the *PAH* gene.[2] PAH converts 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 $\geq$ 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).

POLICY STATEMENT

Prior Authorization is recommended for prescription 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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

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 and ii):
     - **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); 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.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Sephience is not recommended in the following situations:

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.

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.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	07/30/2025
Selected Revision	**Phenylketonuria:** For a patient currently receiving Sephience, "patient has achieved a blood phenylalanine concentration ≤ 360 micromol/L" was added as an option for the requirement of having had a clinical response. **Conditions Not Recommended for Approval:** For concurrent use with sapropterin, added Zelvysia to the list of sapropterin products.	10/29/2025