Iowa PDL New Drug Review

Proprietary Name: Sephience®
Common Name: sepiapterin
PDL Category: Endocrine Metabolic Agents

Pharmacology/Usage: Sepiapterin, the active ingredient of Sephience®, is a phenylalanine hydroxylase (PAH) activator. It is a precursor of the enzymatic co-factor tetrahydrobiopterin (BH4) which activates PAH.

Indication: 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.

There is no pregnancy category for this medication; however, the risk summary indicates that the available data on use during pregnancy are not sufficient to assess for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Uncontrolled blood Phe concentrations before and during pregnancy are associated with an increased risk of adverse pregnancy outcomes and fetal adverse effects. The safety and efficacy of use in the pediatric population younger than 1 month of age have not been established.

Dosage Form: Oral Powder, in unit-dose packets: 250mg or 1,000mg.

If the Sephience® liquid or soft food mixture is not administered immediately, cover and store the mixture at controlled room temperature (between 20 to 25 degrees C) for up to 6 hours or refrigerate for up to 24 hours. If the liquid or soft food mixture is stored, stir for at least 30 or 60 seconds, respectively, prior to administration of the prescribed dose. Discard unused Sephience® mixture after 6 hours at controlled room temperature or after 24 hours if refrigerated.

Recommended Dosage: Important recommendations prior to treatment:

- Treatment with Sephience® should be directed by physicians knowledgeable in the management of PKU.
- 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®.
- Obtain baseline blood Phe concentration before starting treatment.
- All patients with PKU who are treated with Sephience® should be on a dietary protein and Phe-restricted diet that is based on blood Phe levels. Patients should undergo regular dietary assessments, including protein and Phe intake, by their healthcare provider.

The recommended starting dosage is based on the patient's age and is administered orally once daily. Administer with food. Refer to the table below, which was adapted from the prescribing information.

Age	Sephience® (mg/kg) per day*
Less than 6 months	7.5mg/kg
6 months to less than 1 year	15mg/kg

Age	Sephience® (mg/kg) per day*
1 year to less than 2 years	30mg/kg
2 years and older	60mg/kg

* 60mg/kg is the maximum daily dose for all patients.

For calculated daily doses less than 1,000mg, the final concentration of prepared Sephience® liquid mixture is 25mg/ml.

For dosage titration in patients less than 2 years of age: After initiating treatment at the starting dosage by age, check blood Phe levels to determine response to treatment within 2 weeks. If blood Phe does not decrease, Sephience® dosage may be titrated incrementally based on blood Phe levels to a maximum daily dosage of 60mg/kg. Existing dietary protein and Phe intake should not be modified during the evaluation period.

Discontinue Sephience® in patients whose blood Phe does not decrease after 2 weeks of treatment at the maximum daily dosage of 60mg/kg.

Regarding dosage modification and monitoring, monitor blood Phe levels during treatment, and if needed, modify the daily dosage of Sephience® within the range of 7.5mg/kg to 60mg/kg and/or dietary protein and Phe intake to ensure adequate blood Phe level control. Frequent blood Phe monitoring is recommended in the pediatric population.

A missed dose should be taken as soon as possible but 2 doses should not be administered on the same day. Resume the normal dosing schedule the following day.

Refer to the prescribing information for additional information regarding preparation and administration instructions.

Drug Interactions: Avoid concomitant use of drugs known to inhibit folate synthesis dihydrofolate reductase (DHFR; e.g., trimethoprim, methotrexate, trimetrexate, pemetrexed, pralatrexate, raltitrexed, and piritrexim) while taking Sephience®. Concomitant administration of such drugs may reduce sepiapterin metabolism to tetrahydrobiopterin (BH4). If concomitant use is not avoidable, monitor blood Phe levels.

Avoid concomitant use of sepiapterin reductase (SR) inhibitors with Sephience®. Concomitant administration of such drugs may reduce sepiapterin metabolism to BH4. If concomitant use is not avoidable, monitor blood Phe levels.

Sephience® may increase the availability of tyrosine, a precursor of levodopa. Neurologic events were reported post marketing in patients receiving another PAH activator and levodopa concomitantly for a non-PKU indication. Monitor patients for a change in neurologic status when levodopa is administered with Sephience®.

Sephience® and PDE-5 inhibitors induce vasorelaxation, thus concomitant use of Sephience® with PDE-5 inhibitors may reduce blood pressure even further. Monitor for signs and symptoms of hypotension with concomitant use of Sephience® with drugs that affect nitric oxide-mediated vasorelaxation (e.g., PDE-5 inhibitors such as sildenafil, vardenafil, or tadalafil).

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Sephience®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included diarrhea (5%), headache (5%), abdominal pain (3%), hypophenylalaninemia (4%), feces discoloration (4%), and oropharyngeal pain (2%). Adverse reactions were similar across both adult and pediatric populations except for hypophenylalaninemia.

Sephience® may increase the risk of bleeding. Bleeding events, including superficial hematomas, prolonged bleeding, and heavy menstrual bleeding have occurred in patients treated with Sephience®. One patient with non-traumatic superficial hematomas and prolonged bleeding was re-challenged at a lower dose of Sephience® with recurrence of symptoms, which led to treatment discontinuation. The patient experienced symptoms 15 days after initial exposure and two days after rechallenge. The patient had normal blood counts and coagulation studies at the time of the bleeding. Inform the patient about the increased risk of bleeding associated with Sephience® and to follow up with a healthcare provider if any signs of increased bleeding occur. Consider treatment interruption with Sephience® in patients with active bleeding.

In clinical trials of Sephience®, some pediatric PKU patients experienced hypophenylalaninemia (low blood Phe), including some with multiple low blood Phe levels, during Sephience® treatment. Prolonged levels of blood Phe that are too low have been associated with catabolism and endogenous protein breakdown, which has been associated with adverse developmental outcomes. Monitor blood Phe levels during treatment and if needed, modify the Sephience® dosage and/or dietary protein and Phe intake to ensure adequate blood Phe level control. Frequent blood Phe monitoring is recommended in the pediatric population.

In a 10-year post-marketing safety surveillance program for a non-PKU indication using another drug that is a PAH activator, 3 patients with underlying neurological disorders experienced seizures, exacerbation of seizures, over-stimulation, and irritability during co-administration with levodopa. Monitor patients who are receiving levodopa for changes in neurological status during Sephience® treatment.

Contraindications: There are no contraindications listed with this product.

Manufacturer: PTC Therapeutics

Analysis: The efficacy of Sephience® was assessed in Trial 1, a two-part trial that included adult and pediatric patients diagnosed with PKU with hyperphenylalaninemia with at least 2 blood Phe measurements ≥600µmol/L. Included patients in the trial were 54% male, 90% White, and with a mean age of 17 years (range 1 to 61). At trial baseline, 8% of patients had blood Phe levels at <360µmol/L, 36% at 360-600µmol/L, 48% at 600-1200µmol/L, and 8% at >1200µmol/L.

In Part 1, patients (N=157) received open-label treatment with Sephience® for 14 days. In this part of the trial, 66% of PKU patients demonstrated 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 manner to either Sephience® (N=49) or placebo (N=49) 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 this part of the trial, 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 of Trial 1, 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. The following table, adapted from the prescribing information, presents a reduction in blood Phe level from baseline to weeks 5 and 6 in Part 2 of Trial 1 for Sephience®-treated patients relative to placebo.

	Sephience® (N=49)	**Placebo (N=49)**
Baseline Blood Phe Level (µmol/L)		
Mean	646.1	654
Percentiles (25^{th}, 75^{th})	468.5, 769.5	466, 796

	Sephience® (N=49)	Placebo (N=49)
Weeks 5 and 6		
Mean	236	637.9
Percentiles (25th, 75th)	127.7, 291	453, 776
Mean Change in Blood Phe from Baseline to weeks 5 and 6 (µmol/L)		
Adjusted Mean *	-415.8	-19.9
Percentiles (25th, 75th)	-544, -296.7	-86.7, 63.7
Treatment difference in adjusted mean *	-395.9	
Mean Percent Change in Blood Phe from Baseline to weeks 5 and 6 (%)		
Mean	-62.8	1.4
Percentiles (25th, 75th)	-76.9, -60.7	-12.4, 15
Treatment difference in adjusted mean	-64.2	

*Adjusted mean and standard error, p-value <0.0001 for treatment difference were from a mixed model for repeated measures (MMRM) with change in blood Phe from baseline to post-baseline assessments as the response variable, and fixed effects for treatment, baseline blood Phe, baseline Phe stratum, visit and treatment-by-visit interaction.

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 adults and 104 pediatric patients (median age: 14 years, range 2 months to 55 years) received Sephience® treatment. 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 311.4µmol/L and the mean absolute change in Phe from baseline to weeks 1 and 2 in this age group was -125µmol/L.

Place in Therapy: Sephience® is a phenylalanine hydroxylase (PAH) activator 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, and should be administered once daily with food. Treatment with Sephience® should be directed by physicians knowledgeable in the management of PKU. Obtain baseline blood Phe concentration before starting treatment. Efficacy was assessed in Trial 1, a two-part trial that included adult and pediatric patients diagnosed with PKU with hyperphenylalaninemia with at least 2 blood Phe measurements ≥600µmol/L. In Part 2, the double-blind portion, 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. The adjusted mean change was statistically significant between treatment groups, in favor of Sephience®.

Summary

It is recommended that Sephience® should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Sephience [package insert]. Warren, NJ: PTC Therapeutics, Inc; 2025.