

**Product Monograph**  
**Including Patient Medication Information**

<sup>Pr</sup>**SEPHIENCE™**

Sepiapterin for oral suspension

Powder

For Oral Use

250 mg and 1000 mg sepiapterin

Alimentary Tract and Metabolism Products

PTC Therapeutics International Limited  
Dublin 4, D04EE70, Ireland

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## Recent Major Label Changes

None at the time of the most recent authorization.

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*Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.*

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## Part 1: Healthcare Professional Information

### 1. Indications

SEPHIENCE™ (sepiapterin for oral suspension) 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 indicated in conjunction with a phenylalanine (Phe)-restricted diet. (See [4.1 Dosing Considerations](#)).

#### 1.1. Pediatrics

**Pediatrics (<18 years of age):** Based on the data submitted and reviewed by Health Canada, the safety and efficacy of SEPHIENCE in pediatric patients aged 1 month and older have been established. Safety and efficacy have not been established in patients < 1 month of age. (See [7.1.3 Pediatrics](#), [10.3 Pharmacokinetics](#), [Table 7](#) and [14 Clinical Trials](#)).

#### 1.2. Geriatrics

**Geriatrics (≥65 years of age):** The safety and efficacy of SEPHIENCE in patients 65 years of age and older have not been established. Clinical studies of SEPHIENCE did not include patients 65 years of age and older to determine if they respond differently from younger adult patients. Caution should be exercised when prescribing in patients 65 years of age and older.

### 2. Contraindications

SEPHIENCE is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container (see [6 Dosage Forms, Strengths, Composition and Packaging](#)).

### 4. Dosage and Administration

#### 4.1. Dosing Considerations

Treatment with SEPHIENCE should be directed by a healthcare provider experienced in the treatment of PKU. Baseline blood Phe concentration should be obtained before initiating treatment (see [7 Monitoring and Laboratory Tests](#)).

**SEPHIENCE Responsiveness Test:** Response to treatment with SEPHIENCE should be assessed during an evaluation period of 14 consecutive days during which dietary protein and phenylalanine intake must be held constant. Discontinue SEPHIENCE in patients whose blood Phe levels do not decrease after 14 consecutive days of treatment at the maximum daily dose (see [4.2 Evaluation Period](#)).

Controlled efficacy and safety data supported use in patients who were deemed responsive after receiving sepiapterin for 14 days.

Biochemical response to SEPHIENCE treatment cannot reliably be pre-determined by laboratory testing (i.e. molecular testing).

**Dietary Control:** Patients with PKU who are treated with SEPHIENCE should be on a Phe-restricted diet as directed by their healthcare provider based on assessment of blood Phe concentration. Patients should undergo regular assessments, including Phe intake, by their healthcare provider (see [7 Monitoring and Laboratory Tests](#)).

## 4.2. Recommended Dose and Dosage Adjustment

The recommended starting dosage of SEPHIENCE, to be administered orally once daily, is based on age and body weight (Table 1). The maximum recommended dose is 60 mg/kg/day. Blood Phe levels should be monitored regularly during treatment, particularly in pediatric patients. If necessary, adjust the daily dose of SEPHIENCE within the range of 7.5 mg/kg to 60 mg/kg and/or dietary protein and Phe intake to ensure adequate blood Phe level control (see 7 Monitoring and Laboratory Tests and 7 Hypophenylalaninemia).

**Table 1: Recommended Starting Dose of SEPHIENCE<sup>a</sup> Based on Patient's Age and Body Weight**

Age	Recommended Dose of SEPHIENCE per day <sup>b</sup>
<6 months	7.5 mg/kg/day
6 to <12 months	15 mg/kg/day
12 months to <2 years	30 mg/kg/day
≥2 years	60 mg/kg/day <sup>c</sup>

<sup>a</sup> For calculated daily doses less than 1,000 mg, the final concentration of prepared SEPHIENCE liquid mixture is 25 mg/mL (see 4.4 Administration)

<sup>b</sup> 60 mg/kg is the maximum daily dose for all patients

<sup>c</sup> 60 mg/kg dose is the recommended starting dose and maximum dose for patients aged ≥2 years

### Evaluation Period:

*Dosage Titration in Patients Less than 2 Years of Age:* After initiating treatment at the starting dosage by age (Table 1), check blood Phe levels to determine response to treatment within 2 consecutive weeks. If blood Phe does not decrease, SEPHIENCE dosage may be titrated incrementally (as per dose increments in Table 1) based on blood Phe levels up to a maximum daily dosage of 60 mg/kg. During the evaluation period, existing dietary protein and Phe intake should not be modified and patients should be closely monitored for safety.

*Discontinuation for Lack of Biochemical Response:* Discontinue SEPHIENCE in patients whose blood Phe does not decrease after 2 consecutive weeks of treatment at the maximum daily dosage of 60 mg/kg.

## 4.3. Reconstitution

*For patients < 6 months of age,* SEPHIENCE oral powder should only be mixed in water. Do not mix with soft foods, such as apple sauce or strawberry jam, or with apple juice.

*For patients ≥6 months to < 2 years of age,* SEPHIENCE oral powder should be mixed in water or apple juice.

*For patients ≥ 2 years of age* SEPHIENCE oral powder should be mixed in water, apple juice, or a small amount of soft food (such as apple sauce or strawberry jam).

The powder should be mixed well for at least 30 seconds with water or apple juice and for at least 60 seconds with soft food. Once mixed, the dose should be administered immediately (see 4.4. Administration).

If not administered immediately, the liquid or soft food mixtures can be administered within 6 hours

when stored at controlled room temperature between 20°C to 25°C or within 24 hours when stored in the refrigerator (2°C to 8°C). Before administration, the liquid or soft food mixture should be stirred once again for at least 30 seconds and 60 seconds, respectively (see [11 Storage, Stability and Disposal](#)).

#### 4.4. Administration

SEPHIENCE oral powder is available in individual sachets of 250 mg or 1000 mg.

SEPHIENCE should be administered orally once a day with food using mg/kg/day dosing.

An accurate measuring device (e.g., oral dosing syringe or medicine cup) with suitable graduations should be used to ensure administration of the appropriate volume of liquid mixture.

#### Doses Less Than 1,000 mg (administration based on 25 mg/mL concentration)

- Determine the required number of SEPHIENCE sachets and the required volume of water or apple juice to achieve a concentration of 25 mg/mL mixture (see [Table 2](#)).

**Table 2: Number of SEPHIENCE Sachets and Volume to Prepare a SEPHIENCE Mixture of 25 mg/mL for Doses Less than 1,000 mg**

Daily Dose (mg)	Number of 1,000 mg sachets <sup>a</sup>	Number of 250 mg sachets <sup>a</sup>	Volume of water or apple juice (mL) <sup>b</sup>
250 mg or less	0	1	9 mL
251 mg to 500 mg	0	2	18 mL
501 mg to 750 mg	0	3	27 mL
751 mg to 999 mg	1	0	36 mL

Legend: mg = milligrams; mL = milliliters

<sup>a</sup> For calculated daily doses less than 1,000 mg, round the dose *up* to the nearest 250 mg to determine the number of SEPHIENCE sachets and prepare each 250 mg sachet with 9 mL of water or apple juice.

<sup>b</sup> Patients younger than 6 months of age should only use water to mix with SEPHIENCE.

- Calculate the prescribed dose volume to the nearest 0.2 mL.
  - Divide the calculated daily dose (mg) by the final concentration (25 mg/mL) of SEPHIENCE liquid mixture for doses less than 1,000 mg.
  - ***Prescribed dose volume (mL)*** =  $\frac{\text{SEPHIENCE calculated dose (mg)}}{25 \text{ mg/mL}}$
- Prepare a liquid mixture.
  - Open and empty the entire content of each SEPHIENCE sachet into an appropriate-size container and mix with the required volume of water or apple juice as per Table 2.
  - Stir the contents for 30 seconds or more until the mixture is uniformly mixed.
  - Using a graduated oral dosing syringe, draw up the prescribed dose volume to the nearest 0.2 mL from the mixture.

- Administer the prescribed dose volume (mL).
  - Administer immediately.
  - If particles are remaining in the syringe, draw up additional water or apple juice and administer the contents immediately. Repeat if particles still remain.
  - Discard unused portion of SEPHIENCE mixture remaining in the container.
  - Consume additional food after administration of the prescribed dose volume.

**Doses 1,000 mg or Greater (whole sachet administration)**

- Determine the required number of SEPHIENCE sachets and the required volume of water, apple juice, strawberry jam, or applesauce (see [Table 3](#)).

**Table 3: Number of SEPHIENCE Sachets and Volume to Prepare a SEPHIENCE Mixture for Doses of 1,000 mg or Greater**

Daily Dose (mg)	Number of 1,000 mg sachets <sup>a</sup>	Number of 250 mg sachets <sup>a</sup>	Volume of water, apple juice, strawberry jam, or applesauce <sup>b</sup>
1,000 mg to 1,124 mg	1	0	2 Tbsp or 30 mL
1,125 mg to 1,374 mg	1	1	4 Tbsp or 60 mL
1,375 mg to 1,624 mg	1	2	
1,625 mg to 1,874 mg	1	3	
1,875 mg to 2,124 mg	2	0	
2,125 mg to 2,374 mg	2	1	6 Tbsp or 90 mL
2,375 mg to 2,624 mg	2	2	
2,625 mg to 2,874 mg	2	3	
2,875 mg to 3,124 mg	3	0	
3,125 mg to 3,374 mg	3	1	8 Tbsp or 120 mL
3,375 mg to 3,624 mg	3	2	
3,625 mg to 3,874 mg	3	3	
3,875 mg to 4,124 mg	4	0	
4,125 mg to 4,374 mg	4	1	10 Tbsp or 150 mL
4,375 mg to 4,624 mg	4	2	
4,625 mg to 4,874 mg	4	3	
4,875 mg to 5,124 mg	5	0	
5,125 mg to 5,374 mg	5	1	12 Tbsp or 180 mL
5,375 mg to 5,624 mg	5	2	
5,625 mg to 5,874 mg	5	3	
5,875 mg to 6,124 mg	6	0	

Legend: mg = milligrams; mL = milliliters; Tbsp = tablespoons

<sup>a</sup> For calculated daily doses 1,000 mg or greater, round the dose to the nearest 250 mg to determine the number of SEPHIENCE sachets required.

<sup>b</sup> For each 1,000 mg sachet, add 2 Tbsp (30 mL) of water, apple juice, strawberry jam, or applesauce, and then add an additional quantity of 2 Tbsp (30 mL) for up to three 250 mg sachet(s) and then mix.

- Prepare a liquid or soft food mixture.
  - Open and empty the entire content of each SEPHIENCE sachet into a container.
  - Mix with the required amount of water, apple juice, strawberry jam, or applesauce per [Table 3](#).
  - Stir the contents for 30 seconds or more when mixing SEPHIENCE with water or apple juice or 60 seconds or more when mixing SEPHIENCE with strawberry jam or applesauce until the mixture is uniform.
- Administer the dose.
  - Consume the entire mixture immediately.
  - If particles are remaining in the container, add additional water or juice to the container and administer the contents immediately. Repeat if particles still remain.
  - Consume additional food after administration of the entire mixture.

#### 4.5. Missed Dose

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

#### 5. Overdose

The acute effects of overdose have not been evaluated.

No specific antidote is available for overdose with SEPHIENCE. Treatment of overdose with SEPHIENCE consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

#### 6. Dosage Forms, Strengths, Composition, and Packaging

**Table 4: Dosage Forms, Strengths, Composition, and Packaging**

Route of Administration	Dosage Form/ Strength/Composition	Non-medicinal Ingredients
Oral use	Powder, 250 mg and 1000 mg	Colloidal silicon dioxide, Croscarmellose sodium, Isomalt, Magnesium stearate, Mannitol, Microcrystalline cellulose, Sucralose, Xanthan gum

##### Description

SEPHIENCE oral powder is an immediate-release solid dosage form (yellow to orange powder) available in 250 mg and 1000 mg strengths.

SEPHIENCE oral powder is supplied in single-use, heat-sealed laminated aluminum foil sachet. The

sachet foil is a multilayered structure composed of polyethylene terephthalate, white extruded polyethylene (polyester/foil bond), aluminum foil (moisture barrier), heat-seal ionomeric resin (adhesive).

Each carton contains 30 unit-dose sachets.

## 7. Warnings and Precautions

### General

#### *Dietary Intake*

Patients treated with SEPHIENCE should undergo regular clinical assessments of blood Phe levels by their healthcare provider to determine appropriate dietary Phe intake (see [4.1 Dietary Control](#) and [7 Monitoring and Laboratory Tests](#)).

#### *Hypophenylalaninemia (low blood Phe levels)*

In clinical trials, some patients experienced hypophenylalaninemia (blood Phe levels below level of quantification or <35 µmol/L), including in pediatric patients with multiple low blood Phe levels. Prolonged exposure to low blood Phe concentration has been associated with catabolism and endogenous protein breakdown, which can result in adverse developmental outcomes and impaired neurodevelopmental outcome.

Monitor blood Phe levels during treatment and if needed, modify the dosage of SEPHIENCE and/or dietary protein and Phe intake to ensure adequate blood Phe level control. Frequent blood Phe monitoring is recommended, especially in pediatric patients (see [4.2. Recommended Dose and Dosage Adjustment](#) and [7 Monitoring and Laboratory Tests](#)).

#### *Fructose Intolerance*

Patients with rare hereditary problems of fructose intolerance should not take this medicine due to the isomalt content.

#### *Long-term safety data*

Long-term safety data in patients with PKU are limited, especially in pediatric patients < 2 years of age (see [8 Adverse Reactions](#)).

### Carcinogenesis and Genotoxicity

Based on the non-clinical data, sepiapterin is not genotoxic and no evidence of carcinogenic effects was observed in mice (see [16 Non-Clinical Toxicology](#)).

### Dependence, Tolerance and/or Abuse Liability

The mechanism of action does not indicate that SEPHIENCE has abuse potential. No central nervous system (CNS)- or abuse-related effects were observed at or above therapeutic exposures to sepiapterin. The mode of action does not indicate that SEPHIENCE has abuse potential or would evoke a withdrawal and rebound effect.

### Driving and Operating Machinery

It is not anticipated that SEPHIENCE would affect the ability to drive or operate machinery or cause impairment of mental ability.

## Endocrine and Metabolism

Monitor patients when co-administering SEPHIENCE and medications known to be inhibitors of Dihydrofolate Reductase (DHFR). Co-administering SEPHIENCE with inhibitors of DHFR (i.e., trimethoprim, methotrexate, pemetrexed, pralatrexate, and trimetrexate) may require more frequent monitoring of blood Phe levels because these drugs may inhibit the enzymatic conversion of sepiapterin to BH<sub>4</sub> by inhibiting the enzyme DHFR (see [9.4. Drug-Drug Interactions](#)).

## Hematologic

*Increased Bleeding:* SEPHIENCE may increase the risk of bleeding. Bleeding events, including superficial hematomas, prolonged bleeding, epistaxis and heavy menstrual bleeding have occurred in patients treated with SEPHIENCE. One patient with non-traumatic superficial hematomas and prolonged bleeding was rechallenged 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 patients about the risk of bleeding associated with SEPHIENCE and have patients follow up with their healthcare provider should such a bleeding event occur. Consider SEPHIENCE treatment interruption/ discontinuation in patients with active bleeding (see [8 Adverse Reactions](#)).

## Hepatic/Biliary/Pancreatic

The safety and efficacy of SEPHIENCE in patients with hepatic impairment have not been established.

## Monitoring and Laboratory Tests

Patients treated with SEPHIENCE should have baseline and frequent on-treatment measurements of blood Phe concentration. Dietary protein and Phe intake should be carefully monitored by the healthcare provider to ensure maintenance of blood Phe levels within the desirable range.

## Neurologic

*Interaction with Levodopa:* In a 10-year post-marketing safety surveillance program for a non-PKU indication using another drug that is a phenylalanine hydroxylase (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 treatment with SEPHIENCE (see [9 Drug Interactions](#)).

## Renal

The safety and efficacy of SEPHIENCE in patients with renal impairment have not been established.

## Reproductive Health

- **Fertility**

There are no human data on the effect of sepiapterin on fertility. Reproductive toxicity data revealed no effect on fertility and reproductive function of male and female rats (see [16 Non-Clinical Toxicology](#)).

### 7.1. Special Populations

#### 7.1.1. Pregnancy

There are no adequate and well-controlled studies with SEPHIENCE in pregnancy. In embryo-fetal development studies, oral administration of sepiapterin to pregnant rats and rabbits during organogenesis resulted in no adverse developmental effects, at BH<sub>4</sub> exposure levels up to 7- and 4-fold the human exposure at the maximum recommended human dose (MRHD) of 60 mg/kg/day, respectively (see [16 Non-Clinical Toxicology](#)). Caution should be exercised when prescribing in pregnancy.

#### 7.1.2. Breastfeeding

There are insufficient data to assess the excretion of sepiapterin in human milk, or the risk of adverse events in the breastfed infant. It is unknown if sepiapterin is excreted in human milk. Caution should be exercised because many drugs can be excreted in human milk.

#### 7.1.3. Pediatrics

**Pediatrics (<18 years):** Safety and efficacy of SEPHIENCE in pediatric patients aged 1 month and older have been established. Safety and efficacy have not been established in patients less than 1 month of age (see [10.3 Pharmacokinetics, Table 7](#) and [14 Clinical Trials](#)).

Some pediatric patients experienced hypophenylalaninemia, including multiple low blood Phe levels. Frequent monitoring is recommended to assess blood Phe levels and dietary protein and Phe intake (see [7 Hypophenylalaninemia](#) and [7 Monitoring and Laboratory Tests](#)).

#### 7.1.4. Geriatrics

**Geriatrics (≥65 years):** The safety and efficacy of SEPHIENCE in patients 65 years of age and older have not been established. Clinical studies of SEPHIENCE did not include patients 65 years of age and older to determine if they respond differently from younger adult patients. Caution should be exercised when prescribing in patients 65 years of age and older.

## 8. Adverse Reactions

### 8.1. Adverse Reaction Overview

The safety profile for SEPHIENCE is based on clinical trials in the PKU population, which involved both pediatric and adult patients who received SEPHIENCE at doses ranging from 7.5 to 60 mg/kg/day. In these studies, the age of the patients ranged from 2 months to 61 years. The most frequently reported (≥2%) treatment-related adverse reactions for SEPHIENCE (pooled across Studies PKU-003 and PKU-004) were diarrhea, headache, feces discoloured, vomiting, nausea, upper abdominal pain, and fatigue. Cases of hypophenylalaninemia were observed more frequently in children than adults (see [7 Hypophenylalaninemia](#)).

Five patients discontinued treatment due to adverse reactions, including: anxiety, vomiting, constipation, nausea, headache and hemorrhagic diathesis.

## 8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug.

The safety profile for SEPHIENCE is based on clinical trials in patients with PKU. These data included 222 patients who were exposed to sepiapterin for oral suspension up to 60 mg/kg/day of which: 15 (6.8%) were < 2 years old, 25 (11.3%) were 2 to < 6 years old, 46 (20.7%) were 6 to < 12 years old, 55 (24.8%) were 12 to < 18 years old, and 81 (36.5%) were ≥ 18 years old, and the median duration of treatment (in weeks) was 34.3.

Table 5 below lists adverse reactions that were reported in ≥2% of SEPHIENCE-treated patients at a frequency greater than that of placebo group in Part 2 of Study PKU-003.

**Table 5: Adverse Reactions for SEPHIENCE in Patients With PKU That Occurred in ≥2% of Sepiapterin for Oral Suspension-Treated Patients and More Frequently Than in Placebo (Study PKU-003, Part 2, 6 Week Exposure)**

MeDRA SOC	Adverse Reaction (Preferred Term)	SEPHIENCE N=56 n (%)	Placebo N=54 n (%)
Gastrointestinal disorders	Diarrhea	4 (7.1)	1 (1.9)
	Abdominal pain <sup>a</sup>	3 (5.4)	1 (1.9)
	Feces discoloured	2 (3.6)	0
Nervous system disorders	Headache	4 (7.1)	1 (1.9)
Infections and infestations	Upper respiratory tract infection	3 (5.4)	1 (1.9)
	Influenza	2 (3.6)	1 (1.9)
	Oropharyngeal pain	2 (3.6)	1 (1.9)
Metabolism and Nutrition Disorders	Hypophenylalaninemia	2 (3.6)	0

Legend: PKU = phenylketonuria; SOC = System Organ Class

<sup>a</sup> Includes Abdominal pain, Abdominal pain upper, and Abdominal discomfort.

Long-term safety data are limited.

### 8.2.1. Clinical Trial Adverse Reactions – Pediatrics

Long-term safety data are limited, especially for patients aged 2 years and younger.

A limited number of patients < 2 years of age (N=15) were included in the Phase 3 clinical studies of SEPHIENCE. Adverse reactions were similar across adult and pediatric populations except for hypophenylalaninemia, which occurred more frequently in pediatric patients including some patients with multiple low blood Phe levels (see [7 Hypophenylalaninemia](#) and [1.1 Pediatrics](#)).

### 8.3. Less Common Clinical Trial Adverse Reactions

Blood and lymphatic system disorders: Hemorrhagic diathesis

Reproductive system and breast disorders: Heavy menstrual bleeding

## 9. Drug Interactions

### 9.2. Drug Interactions Overview

In vitro studies indicate that sepiapterin and BH<sub>4</sub> are unlikely to be perpetrators of CYP450-mediated metabolism.

In vitro, sepiapterin did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 or induce CYP1A2, CYP2B6, or CYP3A4.

Concomitant administration of drugs known to inhibit folate synthesis DHFR (i.e., trimethoprim, methotrexate, pemetrexed, pralatrexate, and trimetrexate) may interfere with sepiapterin and BH<sub>4</sub> metabolism. Caution is recommended when using such medicinal products while taking SEPHIENCE (see [7 Endocrine and Metabolism](#)).

The potential for drug interactions in the presence of sepiapterin reductase (SR) has not been investigated clinically. Caution should be exercised when SEPHIENCE is co-administered with SR inhibitors, such as sulfasalazine or sulfamethoxazole.

### 9.3. Drug-Behaviour Interactions

Drug-behavioral interactions have not been established.

### 9.4. Drug-Drug Interactions

#### Effect of co-administered drugs on SEPHIENCE

The drugs listed in [Table 6](#) are based on either drug interaction case reports or studies or potential interactions due to the expected magnitude and seriousness of the interaction.

**Table 6: Established or Potential Drug-Drug Interactions**

Co-administered Drug	Source of Evidence	Effect	Clinical Comment
Drugs known to inhibit folate synthesis DHFR (i.e., trimethoprim, methotrexate, pemetrexed, pralatrexate, and	T	These drugs may inhibit the enzymatic conversion of sepiapterin to BH <sub>4</sub> by inhibiting the enzyme DHFR.	Caution should be exercised when SEPHIENCE is co-administered with DHFR inhibitors (see <a href="#">7 Endocrine and Metabolism</a> ). More

trimetrexate)			frequent monitoring of blood Phe levels is recommended.
SR inhibitors (i.e., sulfasalazine or sulfamethoxazole)	T	These drugs may inhibit the enzymatic conversion of sepiapterin to BH <sub>4</sub> by inhibiting the enzyme SR.	Caution should be exercised when SEPHIENCE is co-administered with SR inhibitors. More frequent monitoring of blood Phe levels is recommended.
Drugs that cause vasodilation, including those administered topically, by affecting nitric oxide (NO) metabolism or action including classical NO donors (e.g. glyceryl trinitrate (GTN), isosorbide dinitrate (ISDN), sodium nitroprusside (SNP), molsidomin), PDE5 inhibitors (sildenafil, vardenafil, or tadalafil) and minoxidil	T	Hypotension	Caution is recommended during concomitant use of SEPHIENCE with all medicinal products that cause vasodilation.  Monitor blood pressure when administering SEPHIENCE with drugs that affect nitric oxide mediated vasorelaxation (e.g. PDE-5 inhibitors).  The combined use of these medications has not been evaluated in humans.
Levodopa	T	Convulsions, exacerbation of convulsions, increased excitability and irritability	Caution should be used with the administration of SEPHIENCE to patients who are receiving levodopa (see <a href="#">7 Neurologic</a> ).

Legend: BH<sub>4</sub>= tetrahydrobiopterin; DHFR = dihydrofolate reductase; SR = sepiapterin reductase T = Theoretical

BCRP inhibitor: Co-administration of curcumin (2 g, single dose, oral), a BCRP inhibitor with sepiapterin for oral suspension (20 mg/kg, single dose, oral), increased the exposure and maximal concentrations of BH<sub>4</sub> by approximately 20.0% and 24.0%, based on AUC<sub>0-inf</sub> and C<sub>max</sub>, respectively and not considered clinically significant.

#### Effect of SEPHIENCE on co-administered drugs

BCRP substrate:

Co-administration of sepiapterin (60 mg/kg, single dose, oral) with rosuvastatin (10 mg, single dose, oral), a BCRP substrate, increased the exposures and maximal concentrations of rosuvastatin by approximately 1.2% and 13.0%, based on AUC<sub>0-inf</sub> and C<sub>max</sub>, respectively and not considered clinically significant.

## 9.5. Drug-Food Interactions

Sepiapterin is recommended to be taken with food (see [4.4 Administration](#) and [10.3 Pharmacokinetics](#)).

## 9.6. Drug-Herb Interactions

Interactions with herbal products have not been established.

## 9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

# 10. Clinical Pharmacology

## 10.1. Mechanism of Action

Sepiapterin is a precursor of the enzymatic co-factor BH<sub>4</sub> which activates the phenylalanine hydroxylase (PAH) enzyme.

## 10.2. Pharmacodynamics

Phenylalanine is a pharmacodynamic biomarker of clinical outcomes in the development of treatments for PKU. Blood Phe concentration was a surrogate primary clinical efficacy endpoint in the pivotal, randomized, controlled, Phase 3 study (PTC923-MD-003-PKU). Data showed that sepiapterin administration was associated with a significant reduction in blood Phe concentration (see [14 Clinical Trials](#)).

### *Cardiac Electrophysiology*

A randomized, partially-blinded, placebo- and positive-controlled, crossover ECG assessment study was performed in 31 healthy adult subjects. They were administered a single oral dose of sepiapterin 60 mg/kg (therapeutic), sepiapterin 120 mg/kg mg (2 times the maximum recommended dose, supratherapeutic), moxifloxacin 400 mg, and placebo. At the therapeutic 60 mg/kg dose, QTc shortening was observed with a maximum mean difference from placebo of -3.2 (90% CI -5.42, -0.94) ms at 6 hr post-dosing. At the supratherapeutic 120 mg/kg dose, QTc shortening was observed with a maximum mean difference from placebo of -2.3 (90% CI -4.50, -0.06) ms at 5 hours post dosing.

## 10.3. Pharmacokinetics

Following oral administration, sepiapterin is quickly absorbed, and the peak plasma concentrations occur in approximately 1 to 3 hours and decline to below limit of quantitation rapidly (generally by 12 hours). High variability was observed in the plasma concentrations of sepiapterin. No accumulation of sepiapterin was observed following repeated dosing.

Plasma sepiapterin is metabolized extensively to form the pharmacologically active metabolite BH<sub>4</sub> and peak BH<sub>4</sub> concentrations are achieved in approximately 4 hours after oral administration of sepiapterin. The apparent terminal half-life for BH<sub>4</sub> is approximately 5 hours. There is no accumulation of BH<sub>4</sub> following repeated daily doses of sepiapterin up to 60 mg/kg for 7 days. Plasma sepiapterin concentrations and exposures were generally less than 2% of BH<sub>4</sub> C<sub>max</sub> and AUC<sub>0-24h</sub>. The pharmacokinetics (AUC<sub>0-24h</sub> and C<sub>max</sub>) of BH<sub>4</sub> are lower by 14.1% and 39.6% in PKU patients compared to healthy volunteers at the 60 mg/kg/day dose administered with a low-fat low-calorie diet.

**Table 7: Summary of sepiapterin and BH<sub>4</sub> pharmacokinetic parameters in PKU patients following oral administration of SEPHIENCE with food\***

Clinical dose of Sepiapterin	7.5 mg/kg/day	15 mg/kg/day	30 mg/kg/day	60 mg/kg/day	60 mg/kg/day	60 mg/kg/day	60 mg/kg/day		
PK Parameter	0 to <6 Months (N=3)	≥6 Months to <12 Months (N=1)	≥1 Year to <2 Years (N=6)	2 to <6 Years (N=18)	≥6 Years to <12 Years (N=32)	≥12 Years to <18 Years (N=40)	≥18 Years (N=60)	Combined Age <2 Years (N=10)	Combined Age ≥2 Years (N=150)
<b>Sepiapterin</b>									
C <sub>max</sub> (ng/mL) [n]	1.21 [1]	- [0]	8.47 (7.26) [2]	1.55 (0.276) [3]	3.47 (3.39) [4]	3.21 (2.40) [6]	2.53 (1.15) [19]	6.05 (6.63) [3]	2.68 (1.76) [32]
T <sub>max</sub> (h) [n]	3.92 [1]	- [0]	2.00 (2.00, 2.00) [2]	1.08 (0.500, 2.00) [3]	1.53 (1.00, 4.00) [4]	1.50 (0.500, 3.82) [6]	1.98 (0.500, 6.00) [19]	2.00 (2.00, 3.92) [3]	1.98 (0.500, 6.00) [32]
AUC <sub>0-24h</sub> (h•ng/mL) [n]	- [0]	- [0]	- [0]	6.03 (4.55) [2]	21.8 (29.8) [4]	14.4 (8.49) [6]	16.7 (14.5) [17]	- [0]	16.2 (15.6) [29]
<b>BH<sub>4</sub></b>									
C <sub>max</sub> (ng/mL) [n]	207 [1]	248 [1]	205 (69.2) [5]	309 (200) [5]	421 (159) [4]	372 (255) [6]	468 (182) [20]	211 (58.8) [7]	423 (197) [35]
T <sub>max</sub> (h) [n]	3.92 [1]	6.17 [1]	4.02 (2.00, 6.00) [5]	3.97 (2.00, 4.00) [5]	4.00 (3.88, 4.00) [4]	3.00 (1.87, 4.02) [6]	4.00 (2.00, 6.00) [20]	4.02 (2.00, 6.17) [7]	4.00 (1.87, 6.00) [35]
AUC <sub>0-24h</sub> (h•ng/mL) [n]	- [0]	2410 [1]	1780 (552) [4]	2880 (1620) [5]	3650 (1410) [4]	3030 (2180) [6]	3850 (1790) [20]	1900 (557) [5]	3550 (1770) [35]
AUC <sub>0-inf</sub> (h•ng/mL) [n]	- [0]	- [0]	2360 [1]	3400 (2100) [3]	4300 (1190) [3]	4060 (2270) [4]	3780 (1240) [13]	2360 [1]	3850 (1460) [23]
T <sub>1/2</sub> (h) [n]	- [0]	- [0]	3.36 [1]	4.35 (0.861) [3]	4.00 (0.759) [3]	5.10 (0.187) [4]	5.49 (1.04) [13]	3.36 [1]	5.08 (1.02) [23]

**Abbreviations:** AUC<sub>0-24h</sub>, area under the concentration-time curve from time zero to 24 hours postdose; AUC<sub>0-inf</sub>, area under the concentration-time curve from time zero extrapolated to infinity; BH<sub>4</sub>, tetrahydrobiopterin; C<sub>max</sub>, maximum observed concentration; max, maximum; min, minimum; SD, standard deviation; T<sub>1/2</sub>, apparent elimination half-life; T<sub>max</sub>, time to maximum observed concentration

Note: Values are presented as arithmetic mean (SD) except for T<sub>max</sub>, which is shown as median (min, max). Square brackets denote n.

\*Limitations of sepiapterin PK data include high variability in sepiapterin plasma concentration estimation and correction factor to account for endogenous sepiapterin was not applied.

## Absorption

Following oral administration of sepiapterin to healthy subjects, both BH<sub>4</sub> C<sub>max</sub> and AUC<sub>0-last</sub> increased approximately dose proportionally in the dose range 5 to 20 mg/kg; however, in the dose range 20 to 60 mg/kg, both BH<sub>4</sub> C<sub>max</sub> and AUC<sub>0-last</sub> increased less than dose proportionally.

### *Effect of Food*

When sepiapterin doses of 20 mg/kg and 60 mg/kg were administered with a low-fat, low-calorie meal, BH<sub>4</sub> exposures were 1.69- and 1.72-fold higher for C<sub>max</sub> and 1.64- and 1.76-fold higher for AUC<sub>0-24h</sub> compared to administration under fasted conditions. When sepiapterin doses of 20 mg/kg and 60 mg/kg were administered with a high-fat, high-calorie meal, BH<sub>4</sub> exposures were 2.28- and 2.23-fold higher for C<sub>max</sub> and 2.57- and 2.91-fold higher for AUC<sub>0-24h</sub> compared to administration under fasted conditions.

## Distribution

Binding of sepiapterin or BH<sub>4</sub> to plasma protein is low, and the majority of sepiapterin and BH<sub>4</sub> in plasma are free to exert pharmacological effects. The plasma protein binding of sepiapterin was 15.4% and BH<sub>4</sub> was 41.3% based on in vitro protein binding studies.

BH<sub>4</sub> apparent volume of distribution is 143 (66) L/kg in adult patients with PKU. In healthy subjects, elevated BH<sub>4</sub> concentration was observed in the cerebrospinal fluid following repeated sepiapterin oral administration of 60 mg/kg for 7 days.

## Metabolism

Sepiapterin is metabolized by SR/carbonyl reductase and DHFR in a 2-step unidirectional process to form BH<sub>4</sub>. The metabolism of BH<sub>4</sub> is presumed to follow the same pathway as endogenous BH<sub>4</sub> entering the regeneration cycle, oxidized to 4 $\alpha$ -hydroxy-tetrahydrobiopterin during the aromatic amino acid hydroxylation, and regenerated to form BH<sub>4</sub> by pterin-4 $\alpha$ -carbinolamine dehydratase and dihydropteridine reductase.

Extensive metabolism of sepiapterin was observed in humans following a single oral dose of <sup>14</sup>C-sepiapterin. The major metabolic pathway involved oxidation/dehydrogenation, reduction/oxidation, oxidative deamination, dehydration, side chain cleavage, methylation, etc., alone or in combination.

## Elimination

Following a single oral dose of <sup>14</sup>C-sepiapterin 4000 mg to adult healthy subjects, a mean of 6.71% dosed radioactivity was recovered in urine and 26.18% in feces, with the combined total recovery of 32.88% by 240 hours. The majority of that radioactivity was recovered within the first 48 hours post dose (28.17%). The total renal clearance of radioactivity derived from <sup>14</sup>C-sepiapterin was 1.536 L/h (25.6 mL/min). Formation of volatile metabolites from sepiapterin in the gastrointestinal tract was confirmed in an in vitro study using human intestinal microbiota. Sepiapterin was a minor component in urine and was one of the prominent radioactive components in feces.

## Special Populations and Conditions

- **Age:** PKU patients aged 2 months and older were included in the Phase 3 clinical studies. Following the administration of the recommended starting doses, younger patients exhibited lower exposure to BH<sub>4</sub> compared to older patients (see [Table 7](#) and [7.1.3 Pediatrics](#)).
- **Sex:** There were no apparent effects of gender on BH<sub>4</sub> plasma exposure.
- **Race and Ethnicity:** Higher exposures to BH<sub>4</sub> were observed for Asian subjects. In the Japanese

ethno-bridging study, 10% to 24% higher  $AUC_{0-last}$  and 14% to 29% higher  $C_{max}$  of BH<sub>4</sub> were observed in Japanese compared to non-Japanese subjects at sepiapterin dose range of 20 to 60 mg/kg. These changes are not clinically significant.

- **Pregnancy and Breast-feeding:** Sepiapterin has not been studied in pregnancy or breast-feeding. It is not known whether sepiapterin is excreted in human milk. Caution should be exercised when prescribing in pregnancy. Caution should be exercised when using sepiapterin during breast-feeding (see [7.1.1 Pregnancy](#) and [7.1.2 Breastfeeding](#)).
- **Hepatic Insufficiency:** The pharmacokinetics and safety of sepiapterin have not been studied in patients with hepatic impairment (see [7 Hepatic/Biliary/Pancreatic](#)).
- **Renal Insufficiency:** The pharmacokinetics and safety of sepiapterin have not been studied in patients with renal impairment (see [7 Renal](#)).

## 11. Storage, Stability, and Disposal

Store at room temperature (15°C to 25°C).

Keep out of reach and sight of children.

### *Shelf-life after preparation*

Each prepared dose is best administered immediately after preparation.

If the SEPHIENCE liquid or soft food mixture is not administered immediately, cover and store the mixture at controlled room temperature between 20°C to 25°C for up to 6 hours or refrigerate between 2°C to 8°C 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.

## Part 2: Scientific Information

### 13. Pharmaceutical Information

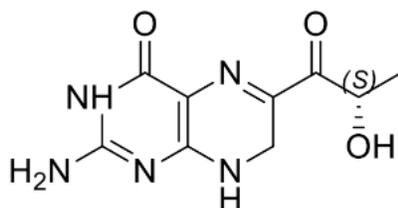
#### Drug Substance

Non-proprietary name of the drug substance: sepiapterin

Chemical name: (S)-2-Amino-6-(2-hydroxypropanoyl)-7,8-dihydropteridin-4(3H)-one

Molecular formula and molecular mass: C<sub>9</sub>H<sub>11</sub>N<sub>5</sub>O<sub>3</sub>; 237.22

Structural formula:



Physicochemical properties: Sepiapterin is a yellow to orange crystalline free base powder. It melts at 223.3°C. Sepiapterin is moderately hygroscopic. At 25°C, a reversible water uptake from 4% to 11% (hysteresis) was observed between 40% and 70% relative humidity (RH). No substantial additional water uptake was observed at 25°C when the RH was increased from 80% to 90%. Sepiapterin is freely soluble in water, methanol, and other organic solvents; soluble in dimethyl acetamide; and sparingly soluble in dimethyl sulfoxide and *N*-methylpyrrolidone. The commercial drug substance is crystalline polymorph Form F, and chirality is (1S)-enantiomer (with one stereogenic center).

### 14. Clinical Trials

#### 14.1. Clinical Trials by Indication

Treatment of hyperphenylalaninemia (HPA) in patients with phenylketonuria (PKU).

#### Trial Design and Study Demographics

The efficacy of SEPHIENCE (sepiapterin) was evaluated in two clinical studies in patients with PKU.

#### Study PKU-003

Study PKU-003 was a two-part, global, double-blind, randomized, placebo-controlled study of 157 patients with PKU, most of whom were on a phe-restricted diet.

Part 1 of the study tested for responsiveness to SEPHIENCE, with 14 days of open-label treatment with SEPHIENCE followed by a minimum of 14 days of SEPHIENCE washout. Patients ≥2 years of age who experienced a ≥15% reduction in blood phenylalanine (Phe) levels were classified as responsive and continued into Part 2 (N=110). In Part 1, 66% of PKU patients showed a biochemical response to SEPHIENCE with a ≥30% reduction in blood Phe level. After the washout period from Part 1, patients were randomized equally (1:1) to either SEPHIENCE, 20 mg/kg daily for Weeks 1 and 2, 40 mg/kg daily for Weeks 3 and 4, 60 mg/kg daily for Weeks 5 and 6 (N=56), or Placebo (N=54) for 6 weeks. The primary efficacy was assessed 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 patients who demonstrated a ≥30% reduction in blood Phe levels during Part 1.

The majority of patients (61.7%) who participated only in Part 1 (assessment of SEPHIENCE responsiveness) were <18 years old. A total of 3 patients (6.4%) were ≥1 year to <2 years old, 23.4% were ≥6 years to <12 years old, and 21.3% were ≥12 years to <18 years old.

Similarly, the majority (65.5%) of patients in Part 2 were <18 years old. There were 10 patients (9.1%), 29 patients (26.4%), and 33 patients (30.0%) who were ≥2 to <6 years old, ≥6 to <12 years old, and ≥12 to <18 years old, respectively. Patients were distributed relatively evenly between the SEPHIENCE and placebo treatment arms across all age groups.

Patients were predominantly White (91.8%). Over half (65.5%) of the 110 patients in Part 2 had PKU diagnosed at birth, and the majority (82.7%) had “biochemically defined” non-classical PKU.

In Part 2, demographics were comparable between patients randomized to the SEPHIENCE and placebo treatment arms.

### **Study PKU-004**

Study PKU-004 is an ongoing, Phase 3, multicenter, open-label study to assess the safety and dietary Phe tolerance during long-term treatment with SEPHIENCE in patients with PKU.

Eligible feeder participants originally included patients aged <2 years who were SEPHIENCE-responsive in Part 1 of Study PKU-003 and patients ≥2 years old who completed Part 2 of Study PKU-003. Eligible non-feeder-controlled patients included those who have not completed a feeder study and have blood Phe concentrations <360 μmol/L at study entry. Eligible non-feeder-uncontrolled patients included those who have not completed a feeder study and have blood Phe concentrations ≥360 μmol/L at study entry.

As of the data cutoff date, a total of 169 patients, including 65 adult and 104 pediatric patients (median age: 14 years, range 2 months to 55 years) were treated with SEPHIENCE. Five patients 2 to < 6 months of age received SEPHIENCE 7.5 mg/kg, 9 patients 12 months to < 2 years of age received SEPHIENCE 30 mg/kg, and 95 patients 2 to < 18 years of age and 60 patients ≥18 years of age received SEPHIENCE 60 mg/kg.

A total of 129 patients have completed 6 months of treatment, while 95 patients have completed 12 months of treatment.

With the exception of the inclusion of the SEPHIENCE-responsive patients <2 years from Part 1 of Study PKU-003, demographics and baseline characteristics were comparable with the pivotal study.

A summary of the study design and patient demographics for the 2 studies are provided in [Table 8](#).

**Table 8: Summary of Patient Demographics for Clinical Trials in PKU Patients**

Study #	Study Design	Dosage, Route of Administration <sup>a</sup> and Duration	Study Subjects (n)	Mean Age (Range)	Sex
Study PKU-003	Phase 3, multicenter, 2-part, double-blind, placebo-controlled, randomized  <u>Part 1:</u> 14-day open label SEPHIENCE assessment of responsiveness  <u>Part 2:</u> Randomization (1:1) to either 6 weeks' SEPHIENCE or placebo (stratification based on baseline blood Phe and % reduction in blood Phe)	<u>Part 1:</u> SEPHIENCE <ul style="list-style-type: none"> <li>• 7.5 mg/kg (0 to &lt;6 months)</li> <li>• 15mg/kg (6 to &lt;12 months)</li> <li>• 30 mg/kg (12 months to &lt;2 years)</li> <li>• 60 mg/kg (≥2 years) for 14 days starting on Day 1</li> </ul> <u>Part 2:</u> SEPHIENCE <ul style="list-style-type: none"> <li>• 20 mg/kg daily for Days 1 to 14 (i.e., Weeks 1 and 2)</li> <li>• 40 mg/kg daily for Days 15 to 28 (i.e., Weeks 3 and 4)</li> <li>• 60 mg/kg daily for Days 29 to 42 (i.e., Weeks 5 and 6).</li> </ul> Matched dose equivalent placebo	<u>Part 1:</u> N=156 (Subjects in Part 1 only: N=47)  <u>Part 2:</u> N=110 (56 in SEPHIENCE arm and 54 in placebo arm)	<u>Part 1:</u> N=47 18.4 years (1-61 years)  <u>Part 2:</u> SEPHIENC E, N=56 16.5 years (2-47 years)  Placebo, N=54 18.4 years (4-54 years)	<u>Part 1:</u> Male: 28 (59.6%) Female: 19 (40.4%)  <u>Part 2:</u> Male: 57 (51.8%) Female: 53 (48.2%)
Study PKU-004	Phase 3: open-label, safety, efficacy, quality of life	7.5, 15, 30, 60 mg/kg for a minimum of 1 year	N=169 <sup>b</sup> (~200 planned) <u>Overall enrollment:</u> <ul style="list-style-type: none"> <li>• 0 to &lt;6 months (n=5)</li> <li>• ≥6 to &lt;12 months (n=0)</li> <li>• ≥1 to &lt;2 years (n=9)</li> <li>• ≥2 to &lt;6 years (n=19)</li> <li>• ≥6 to &lt;12 years (n=32)</li> <li>• ≥12 to &lt;18 years (n=44)</li> <li>• ≥18 years (n=60)</li> </ul>	17.1 years (0.2-55 years)	Male: 85 (50.3%) Female: 84 (49.7%)

Legend: Phe = phenylalanine; PKU = phenylketonuria

<sup>a</sup> Across all PKU studies, SEPHIENCE was orally administered once daily with food.

<sup>b</sup> As of 02 September 2024 data cutoff date.

## Study Results

### Study PKU-003

In Study PKU-003, the primary endpoint of mean change in blood Phe level from baseline to Weeks 5 and 6 was statistically significant for SEPHIENCE versus placebo in the primary analysis population ( $p < 0.0001$ ) (Table 9).

**Table 9: Mean Change in Blood Phe Levels From Baseline to Week 5 and Week 6 in Part 2 (Primary Analysis Set With Phe Reduction From Baseline  $\geq 30\%$  During Part 1), Study PKU-003**

	SEPHIENCE (N=49)	Placebo (N=49)	Difference SEPHIENCE vs Placebo	p value
<b>Baseline<sup>a</sup></b>				
N	49	49		
Mean (SD) ( $\mu\text{mol/L}$ )	646.1 (253.0)	654.0 (261.5)		
<b>Weeks 5 and 6<sup>b</sup></b>				
N	49	49		
Mean (SD) ( $\mu\text{mol/L}$ )	236.0 (174.9)	637.9 (259.9)		
Mean change from baseline ( $\mu\text{mol/L}$ )	-410.1 (204.4)	-16.2 (198.6)		
Mean change from baseline (%)	-62.8%	1.4%		
<b>LS mean estimate for the mean change from baseline</b>				
LS mean (SE)	-415.8 (24.1)	-19.9 (24.2)	-395.9 (33.8)	<0.0001
95% CI	(-463.5, -368.0)	(-68.0, 28.2)	(-463.1, -328.7)	

Legend: CI = confidence interval; LS = least squares; MMRM = mixed model for repeated measures; N = number of patients; Phe = phenylalanine; SD = standard deviation, SE = standard error

<sup>a</sup> Baseline is the average of Day -1 and Day 1 blood Phe levels in Part 2.

<sup>b</sup> Blood Phe concentrations were based on average values during Weeks 5 and 6.

LS means, SEs, CIs, and p values are based on MMRM on change from baseline in blood Phe with treatment, baseline Phe stratum ( $< 600$  or  $\geq 600$   $\mu\text{mol/L}$ ), visit and treatment-by-visit interaction; baseline blood Phe as fixed effects; and a random participant effect with an unstructured covariance matrix.

Of the 35 patients with classical PKU enrolled in Study PKU-003, 16 (45.7%) were determined to have responded to SEPHIENCE ( $\geq 30\%$  reduction in baseline blood Phe levels). An exploratory analysis in this subgroup of patients, showed a mean decrease of 69% in blood Phe from baseline to Week 6 in patients taking SEPHIENCE (N=6), compared to a mean increase of 3.5% in patients taking placebo (N=9).

### Study PKU-004

In the open-label Study PKU-004, supportive efficacy data were provided that suggested in some patients who were carefully monitored and well-controlled within target blood Phe levels ( $\leq 360$   $\mu\text{mol/L}$ ), daily SEPHIENCE administration allowed for an increase in mean daily Phe consumption up to the recommended daily allowance by age and weight.

Across PKU-003 and PKU-004, of the 203 patients  $\geq 2$  years of age, (65%) achieved a  $\geq 30\%$  decrease in blood Phe from baseline at Weeks 1 and 2. Of the 12 patients under the age of 2 years with at least 1 post-baseline efficacy measurement, 8 patients (67%) achieved a  $\geq 30\%$  decrease in blood Phe from baseline at Weeks 1 and 2. The baseline Phe level in patients less than 2 years of age was 362  $\mu\text{mol/L}$  and the mean absolute change in Phe from baseline to Weeks 1 and 2 in this age group was -127.9  $\mu\text{mol/L}$  (standard deviation 277.8  $\mu\text{mol/L}$ ). The mean (SD) percentage of patients  $< 2$  years and  $\geq 2$  years of age who maintained target blood Phe concentration (defined as  $< 360 \mu\text{mol/L}$ ) at any given 2-week interval during Study PKU-004 was 84.2% (19.6) and 74.3% (24.8), respectively.

## 16. Non-Clinical Toxicology

### General Toxicology

In repeat-dose studies, sepiapterin was administered via oral gavage in rats for 26 weeks at doses up to 200 mg/kg/day. Adverse effects were observed in both sexes at doses  $\geq 100$  mg/kg/day, such as renal toxicity, including renal tubular degeneration, interstitial inflammation, and fibrosis as a result of crystal deposition in the papillary collecting tubules. These findings were partially reversible and occurred at doses  $\geq 100$  mg/kg/day corresponding to 3-fold the BH<sub>4</sub> human exposure levels (AUC<sub>0-24h</sub>) at the MRHD. The no observed effect level (NOEL) was 30 mg/kg/day.

Sepiapterin was also administered via oral gavage in marmoset monkeys for 9 months at doses up to 300 mg/kg/day. No renal toxicity was observed at the NOEL of 300 mg/kg/day corresponding to 5-fold the BH<sub>4</sub> human exposure levels (AUC<sub>0-24h</sub>) at the MRHD.

### Carcinogenicity

In a 6-month carcinogenicity study in transgenic CByB6F1-Tg (HRAS)<sup>2Jic</sup> hemizygous mice, sepiapterin did not increase the incidence of tumors in males at dose levels up to 300 mg/kg/day and in females up to 1000 mg/kg/day corresponding, respectively, to 9- and 12-fold the BH<sub>4</sub> human exposure (AUC<sub>0-24h</sub>) levels at the MRHD.

### Genotoxicity

Sepiapterin was not mutagenic with or without metabolic activation in the Ames assay in five bacteria strains. Sepiapterin was clastogenic in the *in vitro* chromosomal aberration assay in cultured human lymphocytes without metabolic activation but not with metabolic activation. Sepiapterin was not mutagenic or clastogenic in the *in vivo* (micronucleus and the comet) assays in rats treated with oral doses up to 2000 mg/kg.

### Reproductive and Developmental Toxicology

In a fertility and early embryonic development (FEED) study in rats, sepiapterin was given prior to and throughout mating in male and female rats and continuing to gestation day (GD) 7 in females at dose levels of 30, 100, and 300 mg/kg/day via oral gavage. No effect on fertility and reproductive function of male and female rats was observed at doses up to 300 mg/kg/day.

In the pre- and post-natal development (PPND) study in rats, sepiapterin was administered at dose levels of 30, 100, and 300 mg/kg/day via oral gavage once daily to pregnant rats from GD 6 to lactation day 20. Sepiapterin did not induce effects on maternal reproductive function or on developmental and reproductive parameters of male and female offspring at doses up to 300 mg/kg/day.

In embryo-fetal development (EFD) studies, sepiapterin was administered at dose levels of 100, 300, and 1,000 mg/kg/day via oral gavage to pregnant rats during the period of organogenesis from GD 7 to GD 17 and to pregnant rabbits from GD 7 to GD 19. There were no maternal or embryo-fetal developmental toxicities at doses up to 1,000 mg/kg/day for pregnant rats and rabbits corresponding, respectively, to 7- and 4-fold the BH<sub>4</sub> human exposure levels (AUC<sub>0-24h</sub>) at the MRHD.

### Juvenile Toxicity

In a 10-week juvenile toxicity (postnatal day [PND]4 through PND70) study, sepiapterin was administered via oral gavage in rats at doses of 0, 5/30, 10/100, and 30/300 mg/kg/day. No sepiapterin-related effects were observed at the NOAEL of 30/300 mg/kg/day corresponding to 3-fold the BH<sub>4</sub> human exposure levels (AUC<sub>0-24h</sub>) at the MRHD.

## Patient Medication Information

### READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr **SEPHIENCE™**

#### **sepiapterin for oral suspension**

This Patient Medication Information is written for the person who will be taking **SEPHIENCE**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **SEPHIENCE**, talk to a healthcare professional.

#### **What SEPHIENCE is used for:**

SEPHIENCE is used to lower blood levels of phenylalanine (Phe) in adults and children 1 month of age and older with phenylketonuria (PKU) who have shown they respond to sepiapterin, the medicinal ingredient in SEPHIENCE. It is used together with a Phe-restricted diet.

Your healthcare professional will test you over a 14 consecutive day evaluation period to determine if SEPHIENCE is right for you.

#### **How SEPHIENCE works:**

Our bodies break down the protein in foods into amino acids. Phenylketonuria (PKU) is an inherited disease where people cannot break down the amino acid phenylalanine (Phe), causing a buildup in the blood and brain, which can be harmful. SEPHIENCE contains the medicinal ingredient sepiapterin, which is used by the body to help break down Phe. This reduces the harmful excess of Phe in the blood.

#### **The ingredients in SEPHIENCE are:**

Medicinal ingredient: sepiapterin

Non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, isomalt, magnesium stearate, mannitol, microcrystalline cellulose, sucralose, and xanthan gum

#### **SEPHIENCE comes in the following dosage forms:**

Powder: 250 mg and 1000 mg

#### **Do not use SEPHIENCE if:**

- you are allergic to sepiapterin or any of the non-medicinal ingredients in SEPHIENCE (see **The ingredients in SEPHIENCE are:**)

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take SEPHIENCE. Talk about any health conditions or problems you may have, including if you:**

- have a rare hereditary intolerance to fructose as SEPHIENCE contains isomalt as a non-medicinal ingredient

- are taking medicines called “dihydrofolate reductase (DHFR) inhibitors” that affect how your body uses the B vitamin folate, such as methotrexate, pemetrexed, pralatrexate, or trimetrexate, which are used for cancer treatment and to treat some immune system disorders
- have liver or kidney problems
- are taking levodopa, used to treat Parkinson’s disease. Taking SEPHIENCE with levodopa can cause over-stimulation, irritability or seizures or make seizures worse.
- are pregnant or planning to become pregnant
- are breastfeeding or planning to breastfeed

**Other warnings you should know about:**

- **Risk of bleeding:** SEPHIENCE can increase your risk of bleeding. This can include bruising or red or purple skin marks, bleeding that lasts longer than usual or does not stop, nose bleeds and heavy menstrual bleeding. If you notice any unusual bleeding while you are taking SEPHIENCE talk to your healthcare professional.
- **Low blood Phe (hypophenylalaninemia):** This is common during treatment and can be severe. Your healthcare professional will check your blood Phe levels before you start taking SEPHIENCE. They will monitor your blood Phe levels along with your dietary protein and Phe intake frequently while you are being treated with SEPHIENCE.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.**

**The following may interact with SEPHIENCE:**

- medicines called “DHFR inhibitors” that are used to suppress the immune system or for treatment of cancer, such as trimethoprim, methotrexate, pemetrexed, pralatrexate, trimetrexate
- medicines called “sepiapterin reductase (SR) inhibitors” used for the treatment of inflammation, such as sulfasalazine, or for the treatment of bacterial infections, such as sulfamethoxazole
- medicines used to prevent and treat chest pain (angina), such as glyceryl trinitrate (GTN), isosorbide dinitrate (ISDN), sodium nitroprusside (SNP), molsidomin
- medicines used to treat erectile dysfunction, such as sildenafil, vardenafil, tadalafil
- minoxidil, used to stimulate hair growth and slow down balding
- levodopa, used to treat Parkinson’s disease

**How to take SEPHIENCE:**

- **Always take this medicine exactly as your healthcare professional has told you.** Check with your healthcare professional if you are not sure.
- **Do not** stop taking SEPHIENCE or change your dose without talking to your healthcare professional, as phenylalanine levels in your blood may increase.
- Your healthcare professional will do blood tests before and during your treatment with SEPHIENCE to check your blood Phe levels.
- Your healthcare professional may change your dose, temporarily stop, or permanently stop treatment with SEPHIENCE if your blood tests show it is not working or if you have certain side effects.
- Your healthcare professional may change your diet during treatment. Follow your healthcare professional’s instructions and do not make any changes to your diet without first talking to your healthcare professional.

- Take SEPHIENCE orally, once daily with food.
- SEPHIENCE can be mixed in water, apple juice, or soft foods such as apple sauce or jam. The dose is based on age and body weight. Your healthcare professional will tell you:
  - which sachet dose to use (250 mg or 1000 mg)
  - the amount of water, apple juice, or soft foods to be added to SEPHIENCE
  - the amount you will need to take for your prescribed dose
- **For patients less than 6 months of age:** SEPHIENCE should be mixed only in water. Do not mix with soft foods, such as apple sauce or strawberry jam, or with apple juice.
- **For patients 6 months to 2 years of age:** SEPHIENCE should be mixed in water or apple juice.
- The powder should be mixed well for at least 30 seconds with water or apple juice and for at least 60 seconds with soft food. Once mixed, the dose should be taken immediately.
- If the dose is not taken immediately, the liquid and soft food mixtures can be used within 6 hours when stored between 20°C and 25°C or within 24 hours when stored in the refrigerator. Before giving the dose, the liquid mixture or soft food mixture should be stirred once again for at least 30 seconds or 60 seconds, respectively.
- An accurate measuring device (e.g. oral dosing syringe or medicine cup) with suitable graduations should be used to make sure the dose contains the appropriate volume of liquid mixture.
- Please see the **Instructions for Use** at the end of this leaflet for complete instructions on how to prepare and administer SEPHIENCE.

**Usual dose:**

The dose depends on your age and weight in kilograms (kg), and this will be calculated by your healthcare professional who prescribes it for you (or your child).

The starting dose is:

**Children younger than 2 years**

- Under 6 months: 7.5 mg / kg body weight once a day
- Between 6 and 12 months: 15 mg / kg body weight once a day
- Between 12 and 24 months: 30 mg / kg body weight once a day

Some patients may need an increase in their dose. This will be determined by your healthcare professional. The maximum dose is 60 mg / kg.

**Adults and children 2 years of age and older**

- The starting, recommended and maximum dose is 60 mg / kg body weight once a day.

**Overdose:**

If you think you, or a person you are caring for, have taken too much SEPHIENCE, contact a healthcare professional, hospital emergency department, regional poison control center or Health Canada’s toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

**Missed Dose:**

If you missed a dose of this medication, take it as soon as you remember on the same day. Then go back to your normal dosing schedule on the next day. Do not take two doses at the same time.

### Possible side effects from using SEPHIENCE:

These are not all the possible side effects you may have when taking SEPHIENCE. If you experience any side effects not listed here, tell your healthcare professional.

#### Side effects may include:

- diarrhea
- nausea, vomiting
- stomach pain
- unusual-coloured feces (yellow or orange)
- headache
- fatigue

#### Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
<b>Unknown</b>			
<b>Bleeding problems:</b> bruising, red or purple skin marks, bleeding that lasts longer than usual or does not stop, nose bleeds, heavy menstrual bleeding		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

#### Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting ([canada.ca/drug-device-reporting](http://canada.ca/drug-device-reporting)) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

#### Storage:

Store at room temperature (15°C to 25°C).

Keep out of reach and sight of children.

After mixing the medicine, take it immediately. If not, the solution or mixture may be covered and stored up to 24 hours in the refrigerator (2°C to 8°C) or up to 6 hours between 20°C and 25°C.

Discard unused SEPHIENCE solution or mixture after 6 hours between 20°C and 25°C or after 24 hours if refrigerated.

**If you want more information about SEPHIENCE:**

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website: (Drug Product Database: Access the database); or by calling 1-866-899-7002.

This leaflet was prepared by PTC Therapeutics International Limited.

Date of Authorization: 2025-10-07

**INSTRUCTIONS FOR USE**  
**SEPHIENCE (seh-FIGH-ence)**  
**sepiapterin for oral suspension**

This Instructions for Use contains information on how to prepare, take, or give SEPHIENCE.

Ask your healthcare professional if you have any questions on how to prepare, take, or give SEPHIENCE.

**The preparation steps differ based on the prescribed dose. Follow the steps specific to the dose your healthcare professional has prescribed. See the section called:**

- **Instructions for SEPHIENCE Doses Less Than 1,000 mg or**
- **Instructions for SEPHIENCE Doses 1,000 mg or Greater**

**Each SEPHIENCE carton contains:**

- 30 SEPHIENCE 250 mg dose sachets **or**
- 30 SEPHIENCE 1,000 mg dose sachets

**Important information you need to know before taking or giving SEPHIENCE:**

- SEPHIENCE comes as a sachet containing powder.
- Take or give SEPHIENCE exactly as your healthcare professional tells you.
- Be sure that you know what dose of SEPHIENCE your healthcare professional has prescribed. Your healthcare professional will prescribe SEPHIENCE 250 mg sachet(s), SEPHIENCE 1,000 mg sachet(s), or both types of sachets to prepare your dose.
- Your healthcare professional may change your dose of SEPHIENCE depending on how you respond to treatment and based on your weight and age.
- Take or give SEPHIENCE 1 time each day with food. You must take or give more food after each SEPHIENCE dose.
- **Do not** use SEPHIENCE sachet(s) after the expiration date on the sachet(s) and box. The expiration date is the last day of the expiration month.
- **For SEPHIENCE doses less than 1,000 mg:** SEPHIENCE is to be mixed with water or apple juice before taking or giving. Follow the section called **Instructions for SEPHIENCE Doses Less Than 1,000 mg**.
- **For SEPHIENCE doses 1,000 mg or greater:** SEPHIENCE can be mixed with water, apple juice, strawberry jam, or applesauce before taking or giving. Follow the section called **Instructions for SEPHIENCE Doses 1,000 mg or Greater**.

## Instructions for SEPHIENCE Doses Less Than 1,000 mg:

### How to prepare SEPHIENCE mixture for doses less than 1,000 mg:

- The dose of SEPHIENCE is based on body weight. This will change as your child grows. Your healthcare professional will tell you:
  - the number of SEPHIENCE sachets needed for one dose,
    - For patients less than 6 months of age, SEPHIENCE should only be mixed in water.
    - For patients 6 months to 2 years of age, SEPHIENCE should be mixed in water or apple juice.
  - the amount of water or apple juice needed to mix one dose of SEPHIENCE, and
  - the amount of the mixture (powder and water or apple juice) to give your child for their prescribed dose.
- **You may need to measure a smaller amount of mixture than you prepared to take or give the correct prescribed dose of SEPHIENCE.**

### Supplies needed to mix and give SEPHIENCE doses less than 1,000 mg:

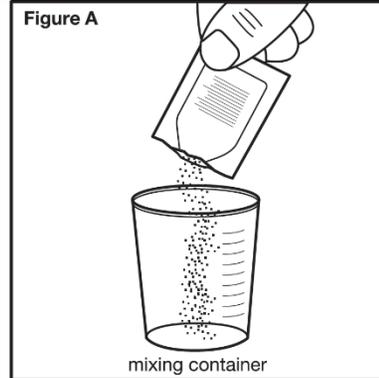
- The number of SEPHIENCE 250 mg sachet(s) needed for 1 dose, or one SEPHIENCE 1,000 mg sachet(s)
- 1 small cup of water **or** apple juice
- 1 mixing container
- 1 small spoon
- a 10 mL oral dosing syringe or recommended oral dosing syringe
- scissors (optional)

Ask your pharmacist for a container for mixing SEPHIENCE and an oral dosing syringe if you do not have these supplies.

**Step 1:** Find a clean, flat work surface. Place the following items on your clean, flat work surface:

- prescribed number of SEPHIENCE sachets for your daily dose
- a small cup of water **or** apple juice
- mixing container
- small spoon
- oral dosing syringe

**Step 2:** Check the label on the SEPHIENCE sachet(s) to make sure you have the number of sachets for the prescribed dose. Open the SEPHIENCE sachet(s) by folding and tearing at the tear notch, or using scissors to cut the sachet(s) open at the dotted line. Empty the entire contents of **each** SEPHIENCE sachet(s) into the mixing container (see **Figure A**).



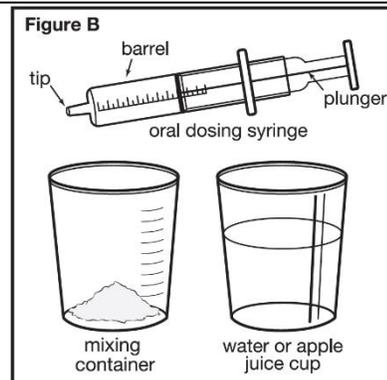
**Step 3:** Place the tip of the oral dosing syringe into the cup containing the water or apple juice. Pull back on the plunger and draw up the amount of water or apple juice needed to prepare the sachet(s) for the prescribed dose.

**Use 9 mL of water (if less than 6 months of age) or 9 mL of water or apple juice (if 6 months to 2 years of age) for each 250 mg sachet.** For example:

- If you are preparing 1 sachet of SEPHIENCE, you will need to add 9 mL of water or apple juice.
- If you are preparing 2 sachets of SEPHIENCE, you will need to add 18 mL of water or apple juice.
- If you are preparing 3 sachets of SEPHIENCE, you will need to add 27 mL of water or apple juice.
- If you are preparing 4 sachets of SEPHIENCE, you will need to add 36 mL of water or apple juice.

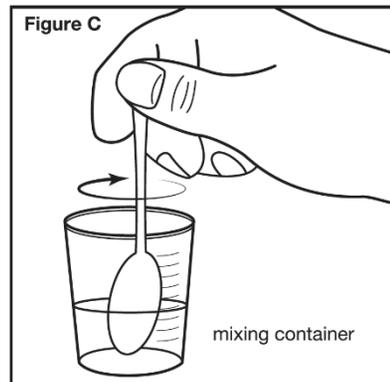
**If you are using one 1,000 mg sachet to prepare the prescribed dose, you will need to add 36 mL of water or apple juice.**

Slowly add the water or apple juice to the mixing container containing the SEPHIENCE powder. Repeat until the entire amount of water or apple juice that is needed to mix the number of SEPHIENCE sachets has been added to the mixing container (see **Figure B**).

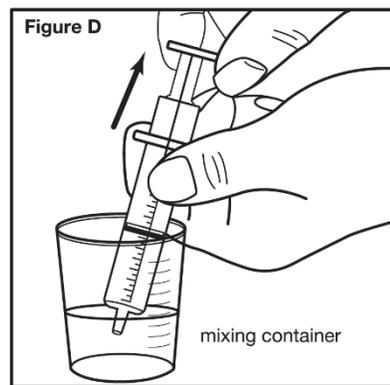


**Step 4:** Stir the SEPHIENCE mixed with water **or** apple juice well for 30 seconds or more with a small spoon until the SEPHIENCE mixture is free of lumps (see **Figure C**).

SEPHIENCE is not expected to dissolve completely. This is normal.



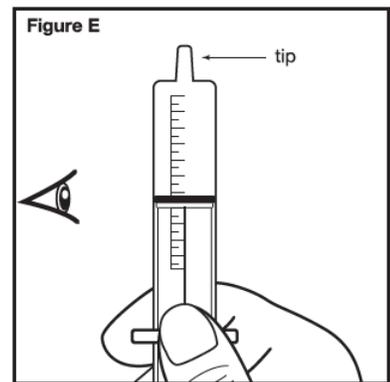
**Step 5:** Place the tip of the oral dosing syringe into the mixture inside the mixing container. Pull back on the plunger until the edge of the plunger lines up with the marking for the dose as instructed by your healthcare professional in mL (milliliters) (see **Figure D**).



**Step 6:** Take the oral dosing syringe out of the mixing container. Carefully turn the oral dosing syringe so that the tip is pointing up. Check the syringe marking to make sure that the amount of SEPHIENCE mixture in the oral dosing syringe lines up with the prescribed SEPHIENCE dose in mL (milliliters) (see **Figure E**).

Your dose may be different than the dose shown in **Figure E**.

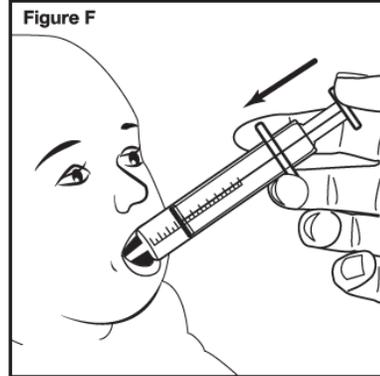
Give SEPHIENCE mixture right away after it is drawn up into the syringe.



**Step 7:** Place the tip of the oral dosing syringe into your child's mouth. Point the tip of the oral dosing syringe toward either cheek (see **Figure F**).

Push on the plunger slowly, until all the mixture in the oral dosing syringe is given.

If the prescribed dose is more than 10 mL, **repeat** Step 5 to Step 7 until you give the **total amount of prescribed dose in mL (milliliters)** by your healthcare professional.



**Step 8:** If there is any mixture left in the oral dosing syringe, draw up more water or apple juice into the oral dosing syringe and give until no mixture is left in the oral dosing syringe.

**Step 9:** Throw away (in household garbage) any SEPHIENCE mixture remaining in the mixing container.

Remove the plunger from the barrel of the oral dosing syringe. Wash the oral dosing syringe and mixing container with warm water and air dry. When the oral dosing syringe is dry, put the plunger back into the barrel. Store the oral dosing syringe and mixing container for the next use.

## Instructions for SEPHIENCE Doses 1,000 mg or Greater:

### How to prepare SEPHIENCE mixture for doses 1,000 mg or greater:

- Your healthcare professional will tell you the number of sachets, and the amount of water, apple juice, strawberry jam, or applesauce needed to mix 1 dose of SEPHIENCE per [Table 1](#) below.

### Supplies needed to mix and take or give SEPHIENCE doses 1,000 mg or greater:

- The number of SEPHIENCE 250 mg sachet(s) and/or SEPHIENCE 1,000 mg sachet(s) needed for 1 dose
- a small cup of water, apple juice, strawberry jam, **or** applesauce
- 1 tablespoon to measure the water, apple juice, strawberry jam, **or** applesauce
- additional small cup of water **or** apple juice to rinse the mixing container
- 1 mixing container
- scissors (optional)

Ask your pharmacist for a container for mixing SEPHIENCE if you do not have one.

**Table 1: Number of SEPHIENCE Sachets to Prepare a SEPHIENCE Mixture for Doses of 1,000 mg or Greater**

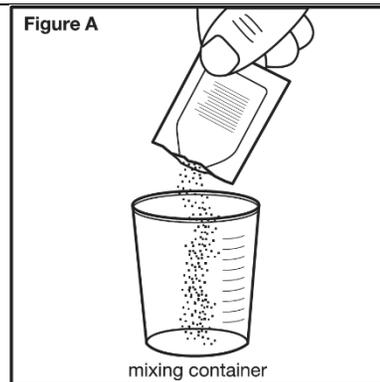
Find your prescribed number of sachets:		Choose one of the following:
Number of 1,000 mg sachets	Number of 250 mg sachets	<ul style="list-style-type: none"> <li>• Water</li> <li>• Apple juice</li> <li>• Strawberry jam</li> <li>• Applesauce</li> </ul>
		Amount of water, apple juice, strawberry jam, <b>or</b> applesauce to mix the sachet(s)
1	0	2 Tbsp or 30 mL
1	1	4 Tbsp or 60 mL
1	2	4 Tbsp or 60 mL
1	3	4 Tbsp or 60 mL
2	0	4 Tbsp or 60 mL
2	1	6 Tbsp or 90 mL
2	2	6 Tbsp or 90 mL
2	3	6 Tbsp or 90 mL
3	0	6 Tbsp or 90 mL
3	1	8 Tbsp or 120 mL
3	2	8 Tbsp or 120 mL
3	3	8 Tbsp or 120 mL

4	0	8 Tbsp or 120 mL
4	1	10 Tbsp or 150 mL
4	2	10 Tbsp or 150 mL
4	3	10 Tbsp or 150 mL
5	0	10 Tbsp or 150 mL
5	1	12 Tbsp or 180 mL
5	2	12 Tbsp or 180 mL
5	3	12 Tbsp or 180 mL
6	0	12 Tbsp or 180 mL

**Step 1:** Find a clean, flat work surface. Place the following items on your clean, flat work surface:

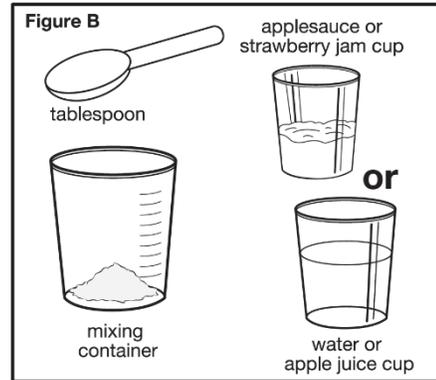
- prescribed number of SEPHIENCE sachets
- a small cup of water, apple juice, strawberry jam, **or** applesauce
- additional small cup of water **or** apple juice to rinse the cup (see **Step 6** below)
- tablespoon
- mixing container

**Step 2:** Check the label on the SEPHIENCE sachet(s) to make sure you have the number of sachets for the prescribed dose. Open the SEPHIENCE sachet(s) by folding and tearing at the tear notch or using scissors to cut the sachet(s) open at the dotted line. Empty the entire contents of **each** SEPHIENCE sachet(s) into the mixing container (see **Figure A**).



**Step 3:** Mix the SEPHIENCE sachet(s) with water, apple juice, strawberry jam, **or** applesauce. See [Table 1](#) above.

Slowly add the water, apple juice, strawberry jam, **or** applesauce to the mixing container containing the SEPHIENCE powder. Repeat until the entire amount of water, apple juice, strawberry jam, **or** applesauce that is needed to mix the number of SEPHIENCE sachets has been added to the mixing container (see **Figure B**).

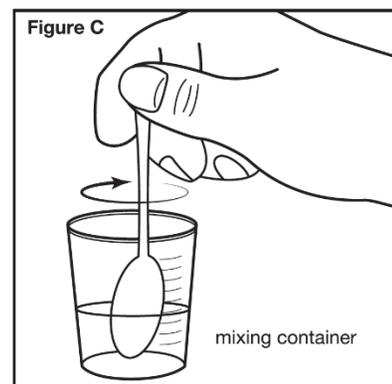


**Step 4:** If you used water or apple juice to mix the SEPHIENCE sachet(s), stir the mixture well for 30 seconds or more with the tablespoon until the SEPHIENCE mixture is free of lumps (see **Figure C**).

SEPHIENCE is not expected to dissolve completely.

**or**

If you used strawberry jam or applesauce to mix the SEPHIENCE sachet(s), stir the mixture well for 60 seconds or more with the tablespoon.



**Step 5:** Give or take all of the SEPHIENCE mixture from the mixing container.

**Step 6:** If any SEPHIENCE mixture remains in the mixing container, rinse the container with water or apple juice (at least 15 mL). Swallow the rinse right away. **Repeat this step until no mixture remains in the mixing container.**

**Step 7:** Wash the mixing container with warm water and air dry. Store the mixing container for the next use.

Manufactured for:

PTC Therapeutics International Limited

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