ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Sephience 250 mg oral powder in sachet
Sephience 1 000 mg oral powder in sachet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sephience 250 mg oral powder in sachet

Each sachet contains 250 mg of sepiapterin.

Sephience 1 000 mg oral powder in sachet

Each sachet contains 1 000 mg of sepiapterin.

Excipient(s) with known effect

Sephience 250 mg oral powder in sachet
Each sachet contains 400 mg of isomalt.

Sephience 1 000 mg oral powder in sachet
Each sachet contains 1 600 mg of isomalt.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral powder.

Yellow to orange powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sephience is indicated for the treatment of hyperphenylalaninaemia (HPA) in adult and paediatric patients with phenylketonuria (PKU).

4.2 Posology and method of administration

Treatment with Sephience must be initiated and supervised by a physician experienced in the treatment of PKU.

Posology

The recommended dose (mg/kg/day) of Sephience to be administered orally once daily is based on age and body weight (see Table 1). The maximum recommended dose is 60 mg/kg/day. The recommended dose of Sephience in patients ≥ 2 years of age is 60 mg/kg/day. However, the dose may be adjusted to a lower dose if the treating physician considers it necessary or appropriate.

Table 1: Recommended dose based on patient's age and body weight

Age	Recommended dose (mg/kg) of Sephience per day
0 to < 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

Tables 2 to 5 below provide dosing information by age group for patients weighing 16 kg or less at different doses (7.5, 15, 30, and 60 mg/kg/day).

Table 2: Recommended dose of Sephience oral powder in sachet by body weight in paediatric patients aged less than 6 months

Dose	**7.5 mg/kg/day**		
Age	**0 to < 6 months**		
Weight (kg)	**Total dose (mg)**	**Number of sachets (250 mg)**	**Administered dose volume (mL) (25 mg/mL)**
2	15	1	0.6
3	22.5	1	0.9
4	30	1	1.2
5	37.5	1	1.5
6	45	1	1.8
7	52.5	1	2.1
8	60	1	2.4
9	67.5	1	2.7
10	75	1	3
11	82.5	1	3.3
12	90	1	3.6
13	97.5	1	3.9
14	105	1	4.2
15	112.5	1	4.5
16	120	1	4.8

Table 3: Recommended dose of Sephience oral powder in sachet by body weight in paediatric patients aged 6 months to less than 12 months

Dose	**15 mg/kg/day**		
Age	**6 months to < 12 months**		
Weight (kg)	**Total dose (mg)**	**Number of sachets (250 mg)**	**Administered dose volume (mL) (25 mg/mL)**
2	30	1	1.2
3	45	1	1.8
4	60	1	2.4
5	75	1	3
6	90	1	3.6
7	105	1	4.2
8	120	1	4.8
9	135	1	5.4
10	150	1	6
11	165	1	6.6
12	180	1	7.2

Dose	**15 mg/kg/day**		
Age	**6 months to < 12 months**		
Weight (kg)	**Total dose (mg)**	**Number of sachets (250 mg)**	**Administered dose volume (mL) (25 mg/mL)**
13	195	1	7.8
14	210	1	8.4
15	225	1	9
16	240	1	9.6

Table 4: Recommended dose of Sephience oral powder in sachet by body weight in paediatric patients aged 12 months to less than 2 years

Dose	**30 mg/kg/day**		
Age	**12 months to < 2 years**		
Weight (kg)	**Total dose (mg)**	**Number of sachets (250 mg)**	**Administered dose volume (mL) (25 mg/mL)**
2	60	1	2.4
3	90	1	3.6
4	120	1	4.8
5	150	1	6
6	180	1	7.2
7	210	1	8.4
8	240	1	9.6
9	270	2	10.8
10	300	2	12
11	330	2	13.2
12	360	2	14.4
13	390	2	15.6
14	420	2	16.8
15	450	2	18
16	480	2	19.2

Table 5: Recommended dose of Sephience oral powder in sachet by body weight in paediatric patients aged 2 years and older

Dose	**60 mg/kg/day**		
Age	**≥ 2 years**		
Weight (kg)	**Total dose (mg)**	**Number of sachets (250 mg)**	**Administered dose volume (mL) (25 mg/mL)**
5	300	2	12
6	360	2	14.4
7	420	2	16.8
8	480	2	19.2
9	540	3	21.6
10	600	3	24
11	660	3	26.4
12	720	3	28.8
13	780	4*	31.2
14	840	4*	33.6
15	900	4*	36
16	960	4*	38.4

* Instead of four 250 mg sachets, one full 1 000 mg sachet can be mixed with 36 mL of water or apple juice. This mixture should be administered with a syringe, according to the administered dose volume detailed in Table 5.

Recommended dose of Sephience oral powder in sachet by body weight for patients 2 years and older and weighing 16 kg or more

The recommended dose is 60 mg/kg/day.
For maintenance doses greater than or equal to 1 000 mg, the calculated daily dose should be rounded to the nearest multiple of 250 mg or 1 000 mg, as appropriate. For instance, a calculated dose of 1 251 to 1 374 mg should be rounded down to 1 250 mg corresponding to 1×250 mg sachet and 1×1 000 mg sachet. A calculated dose of 1 375 to 1 499 mg should be rounded up to 1 500 mg corresponding to 2×250 mg sachets and 1×1000 mg.

Missed dose
A missed dose should be taken as soon as possible. The normal dosing schedule should be resumed the following day.

Discontinuation of treatment

In the pivotal Phase 3 clinical study, a threshold of 15% or greater reduction in blood phenylalanine (Phe) levels was utilised for determination of response.
No controlled efficacy and safety data are available in patients who do not experience a reduction of 15% or greater reduction in blood Phe levels after receiving sepiapterin for 14 days.
The determination of responsiveness for a patient with PKU and the discontinuation of the medicinal product is at the discretion of the treating physician.

Special populations

Elderly
The safety and efficacy of Sephience in patients 65 years of age and older have not been established. Caution should be exercised when prescribing in patients 65 years of age and older.

Renal impairment
The safety and efficacy of Sephience in patients with renal impairment have not yet been established. No data are available (see section 5.2).

Hepatic impairment
The safety and efficacy of Sephience in patients with hepatic impairment have not yet been established. No data are available (see section 5.2).

Paediatric population
In the Phase 3 clinical studies of Sephience, some paediatric patients experienced hypophenylalaninaemia including some patients with multiple low blood Phe levels (see section 4.8).

Method of administration

Oral use.
Sephience should be administered once daily with a meal, using mg/kg dosing.

Sephience oral powder comes in individual sachets of 250 mg or 1 000 mg and should be mixed in water, apple juice, or a small amount of soft food such as apple sauce and jams.

Sephience is intended for long-term use.

Patients weighing less than 16 kg
Sephience should be mixed with water or apple juice (9 mL for each 250 mg sachet; 36 mL for each 1 000 mg sachet), and a portion of this mixture corresponding to a required dose should be administered orally via an oral dosing syringe. The preparation should be mixed well for at least 30 seconds until uniform and free of lumps, before drawing into the dosing syringe. Once mixed, the dose should be administered immediately. If not administered immediately, the liquid mixture can be administered within 6 hours or 24 hours, when stored at room temperature (below 25 °C) or in a refrigerator (2 °C - 8 °C), respectively. The preparation should be mixed once again for at least 30 seconds, before administration. The syringe should be rinsed with additional water or juice (at least 15 mL) to remove any residual and swallowed immediately.

Patients weighing 16 kg or more
Sephience should be mixed with water or apple juice (9 mL for each 250 mg sachet; 20 mL for each 1 000 mg sachet) or soft foods (2 tablespoons total). The preparation should be mixed well for at least 30 seconds with water or apple juice and for at least 60 seconds with soft foods until uniform and free of lumps. Once mixed, administer the dose immediately. If not administered immediately, the liquid and soft food mixtures can be administered within 6 hours or 24 hours when stored at room temperature (below 25 °C) or in a refrigerator (2 °C - 8 °C), respectively. The liquid mixture and soft food mixtures should be mixed once again for at least 30 seconds and 60 seconds, respectively, before administration. The container should be rinsed with additional water or juice (at least 15 mL) to remove any residual and swallowed immediately.

Administration via enteral feeding tube
Sephience oral powder may be administered via an enteral feeding tube 6 Fr or 8 Fr after mixing with water. The manufacturer's instructions for the feeding tube should be followed prior to administering the medicinal product. For instructions on preparation of Sephience before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Dietary intake

Patients treated with Sephience should undergo regular clinical assessments to align with their health care provider on appropriate dietary Phe intake (such as monitoring of blood Phe and tyrosine levels and nutritional intake).

Concomitant use with dihydrofolate reductase (DHFR) inhibitors

Co-administration of sepiapterin with DHFR inhibitors (e.g. trimethoprim, methotrexate, pemetrexed, pralatrexate, and trimetrexate) may require more frequent monitoring of blood Phe levels (see section 4.5).

Long-term safety data

Long-term safety data in patients with PKU are limited (see section 4.8 for adverse reactions evaluated to date for sepiapterin).

Excipients with known effect

Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per sachet, that is to say essentially 'sodium-free'.

Isomalt content
Patients with rare hereditary problems of fructose intolerance should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Sepiapterin reductase (SR) inhibitors

Orally administered sepiapterin is quickly absorbed and rapidly and extensively converted by SR and carbonyl reductase to 7,8-dihydrobiopterin (BH2), which is then unidirectionally converted to BH4 by DHFR. Co-administration of a SR inhibitor is expected to have minimal effect on biotransformation of sepiapterin due to the compensatory effect of carbonyl reductase. Normal blood Phe levels were reported in patients with SR deficiency. Neverthless, caution and more frequent monitoring of blood Phe are recommended when Sephience is co-administered with SR inhibitors, such as sulphasalazine or sulphamethoxazole.

DHFR inhibitors

DHFR mediates the conversion of BH2 to BH4, inhibition of DHFR could potentially result in lower BH4 concentration. However, the impact on sepiapterin concentration is expected to be minimal due to the existence of multiple pathways for the elimination. Caution and more frequent monitoring of blood Phe are required in patients when sepiapterin is co-administered with a DHFR inhibitor, such as trimethoprim, methotrexate, pemetrexed, pralatrexate, and trimetrexate (see section 4.4).

Vasodilatory medicinal products

Caution is recommended during concomitant use of Sephience with medicinal products that cause vasodilation by affecting nitric oxide (NO) metabolism or action, including classical NO donors (e.g. glyceryl trinitrate [GTN], isosorbide dinitrate [ISDN], sodium nitroprusside [SNP], and molsidomin), phosphodiesterase type 5 (PDE-5) inhibitors (e.g. sildenafil, vardenafil, or tadalafil), and minoxidil. In animal studies, BH4 administered orally in combination with a PDE-5 inhibitor had no effect on blood pressure.

Levodopa

Caution should be exercised when prescribing Sephience to patients receiving treatment with levodopa to monitor neurological disorders such as exacerbation of convulsion, increased excitability and irritability, seizures, and exacerbation of seizures.

4.6 Fertility, pregnancy, and lactation

Pregnancy

There are is a limited amount of data from the use of sepiapterin in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). There are no adequate and well-controlled studies with sepiapterin in pregnant women .
As a precautionary measure, it is preferable to avoid the use of Sephience during pregnancy.

Breast-feeding

It is unknown whether sepiapterin/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Sephience therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No clinical studies on the effect on human fertility have been conducted for sepiapterin. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Sephience has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

As presented in the table below, the most frequent adverse reactions were: upper respiratory tract infection (19.8%); headache (15.3%); diarrhoea (14.9%); followed by abdominal pain (12.2%); faeces discoloured (4.5%) and hypophenylalaninaemia (2.7%).

Tabulated list of adverse reactions

The selection of adverse reactions to sepiapterin was based on evidence from clinical trials. The frequency of adverse reactions, as presented below in the tabulated list, was calculated based on pooled data from the 2 pivotal clinical studies in patients with PKU (study PTC923-MD-003-PKU and study PTC923-MD-004-PKU). These data included 222 patients who were exposed to sepiapterin 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 34.286.

Adverse reactions are listed below (Table 6) by MedDRA System Organ Class (SOC). Within each SOC adverse reactions are presented in order of decreasing frequency. Frequencies are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); and not known (cannot be estimated from available data).

Table 6: Adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Very common	Upper respiratory tract infection
Nervous system disorders	Very common	Headache
Gastrointestinal disorders	Very common	Diarrhoea Abdominal pain*
	Common	Faeces discoloured
Metabolism and nutrition disorders	Common	Hypophenylalaninaemia

* Grouping of 3 MedDRA Preferred Terms: Abdominal pain, Abdominal pain upper, Abdominal discomfort.

Paediatric population

Overall, in PKU clinical studies, sepiapterin was well tolerated in paediatric patients. Frequency, type, and severity of adverse reactions in all age groups of paediatric patients were consistent with those in adults. Long-term safety data are limited.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No specific antidote is available for overdose with Sephience. Treatment of overdose with Sephience should consist of supportive medical care including monitoring of vital signs and observation of the clinical status of the patient.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products, Various alimentary tract and metabolism products, ATC code: A16AX28

Mechanism of action

Sepiapterin is a natural precursor of the enzymatic co-factor BH4, a critical co-factor for phenylalanine hydroxylase (PAH). Sepiapterin acts as a dual pharmacological chaperone (sepiapterin and BH4 each with its own binding affinity to variant PAH), including PAH variants commonly found in PKU and known to be insensitive to BH4, to improve the activity of the defective PAH enzyme, achieving a high concentration of BH4 intracellularly. By enhancing the conformational stability of misfolded PAH enzyme and increasing the intracellular concentrations of BH4, sepiapterin is able to effectively reduce blood Phe levels.

Clinical efficacy and safety

The efficacy of sepiapterin was evaluated in three clinical studies in patients with PKU.

Study 1 (PTC923-MD-003-PKU) was a 2-part, global, double-blind, randomised, placebo-controlled clinical study of 157 patients of all ages with PKU.

Part 1 of the study tested for responsiveness to sepiapterin, with 14 days of open-label treatment with sepiapterin followed by a minimum of 14 days of sepiapterin washout. Further, 73.1% (114/156) of study participants demonstrated a ≥ 15% reduction in blood Phe levels in response to sepiapterin. The dose of sepiapterin in patients ≥ 2 years of age was 60 mg/kg/day.

Subjects were instructed to continue their usual diet without modification.
Patients ≥ 2 years of age who experienced a ≥ 15% reduction in blood Phe levels were classified as responsive and continued into Part 2 (n=110). After the washout period from Part 1, patients were randomised equally to either sepiapterin 20 mg/kg/day for Weeks 1 and 2, 40 mg/kg/day for Weeks 3 and 4, 60 mg/kg/day 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 levels from baseline to Weeks 5 and 6 in the sepiapterin-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. In Part 2, demographics were well balanced between the 2 treatment arms (Table 7). The median age at the time of informed consent was 14 years (range: 2-54), and participants, in terms of race, were predominantly white (91.8%). More than half (65.5%) of the 110 participants had PKU diagnosed at birth, and the majority (82.7%) had ‘biochemically defined’ non-classical PKU.

Table 7: Demographics and baseline characteristics

	Participants in Part 1 only (n=47)	Randomised and treated participants in Part 2			Overall treated participants (n=157)
		Sepiapterin (n=56)	Placebo (n=54)	Overall (n=110)	
Age (years)					
n	47	56	54	110	157
Mean (SD)	18.4 (15.07)	16.5 (11.12)	18.4 (10.65)	17.4 (10.88)	17.7 (12.24)
Median (min, max)	15.0 (1, 61)	13.0 (2, 47)	15.0 (4, 54)	14.0 (2, 54)	14.0 (1, 61)
Age category, n (%)					
≥ 1 - < 2 years	3 (6.4)	0	0	0	3 (1.9)
≥ 2 - < 6 years	5 (10.6)	7 (12.5)	3 (5.6)	10 (9.1)	15 (9.6)
≥ 6 - < 12 years	11 (23.4)	17 (30.4)	12 (22.2)	29 (26.4)	40 (25.5)
≥ 12 - < 18 years	10 (21.3)	14 (25.0)	19 (35.2)	33 (30.0)	43 (27.4)
≥ 18 years	18 (38.3)	18 (32.1)	20 (37.0)	38 (34.5)	56 (35.7)

SD, standard deviation

The difference between the 2 treatment groups was statistically significant ($p < 0.0001$) (Table 8).

Table 8: 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 ≥ 30% during Part 1)

	Sepiapterin (n=49)	Placebo (n=49)	Difference sepiapterin vs placebo	p value
Baseline*				
Mean (SD)	646.11 (253.007)	654.04 (261.542)		
Weeks 5 and 6**				
Mean (SD)	236.04 (174.942)	637.85 (259.886)		
Mean change from baseline (µmol/L)	-410.07 (204.442)	-16.19 (198.642)		
Mean percent change from baseline (%)	-62.8%	1.4%		
LS mean estimate for the mean change from baseline				
LS mean (SE)	-415.75 (24.066)	-19.88 (24.223)	-395.87 (33.848)	< 0.0001
95% CI	(-463.52, -367.97)	(-67.97, 28.21)	(-463.07, -328.66)	

CI, confidence interval; LS, least squares; MMRM, mixed model for repeated measures; Phe, phenylalanine; SD, standard deviation; SE, standard error

* Baseline is the average of Day -1 and Day 1 blood Phe levels in Part 2.

** Blood Phe concentrations were based on average values during Weeks 5 and 6.

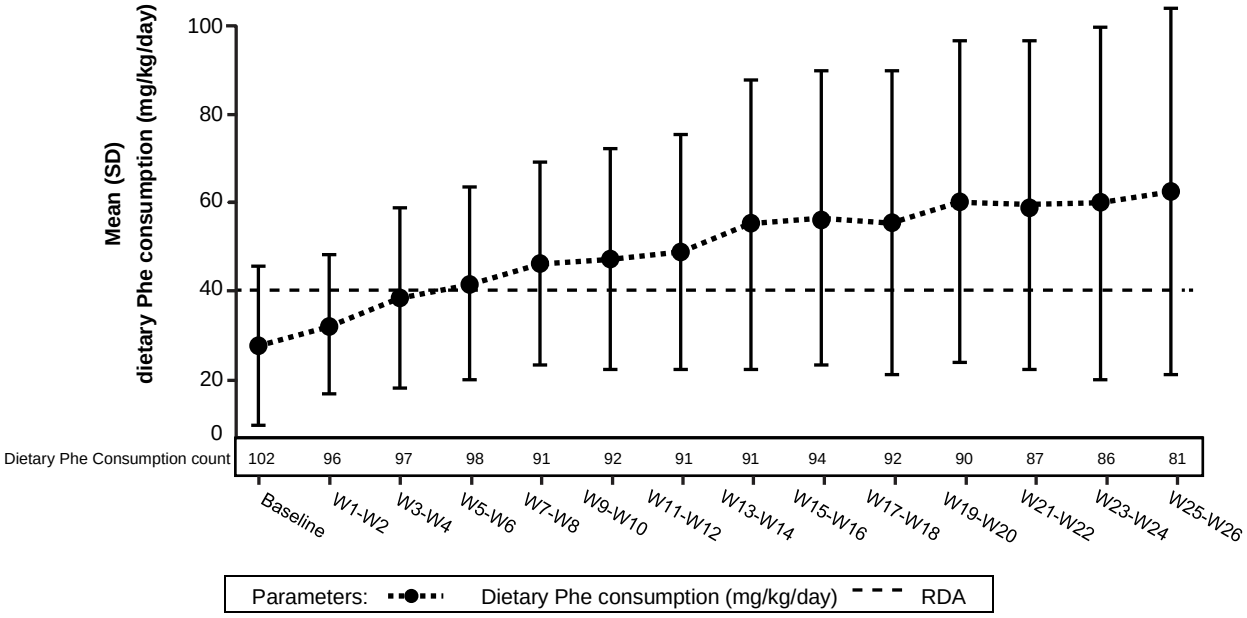
LS means, standard errors, confidence intervals, and p values were from an MMRM with change in blood Phe from baseline to post-baseline assessments as the response variable, and fixed effects for treatment, baseline blood Phe, baseline Phe stratum, visit, and treatment-by-visit interaction.

Similar responses were observed in the population of patients with classical PKU (cPKU), with a 69% reduction in blood Phe at Week 6 in subjects receiving sepiapterin (n=6) versus an increase of 3% after placebo (n=9).

Study 2 (PKU-002) was a Phase 2, randomised, double-crossover, open-label, active-controlled, proof-of-concept clinical study of sepiapterin in patients with PKU.
The study consisted of 6 sequence groups of 4 patients per group for a total of 24 patients. Each sequence group was randomised to receive 7-day treatments of sepiapterin 60 mg/kg/day, sepiapterin 20 mg/kg/day, and sapropterin dihydrochloride 20 mg/kg/day, in random order followed by a 7-day washout after each treatment. Preliminary efficacy was assessed by the reduction in blood Phe concentrations. Results of the primary efficacy weekly mean analysis demonstrated that treatment with sepiapterin resulted in a decrease in blood Phe concentrations relative to baseline that was statistically significant for all treatments (n=24). A greater proportion of patients receiving sepiapterin treatment, regardless of dose, experienced plasma Phe reductions of at least 10%, 20%, and 30% compared with patients receiving sapropterin 20 mg/kg/day. More patients receiving sepiapterin 60 mg/kg/day achieved normalised plasma Phe concentrations (< 120 μmol/L) and blood Phe within the target range (≤ 360 μmol/L) compared with sapropterin 20 mg/kg/day. In subjects with cPKU, treatment with sepiapterin (60 mg/kg/day) resulted in a significant decrease in blood Phe concentration relative to baseline.

Study 3 (PTC923-MD-004-PKU) is an ongoing, Phase 3, multicentre, open-label clinical study to assess the safety and dietary Phe tolerance during long-term treatment with sepiapterin in patients with PKU. One hundred sixty-nine (169) patients received treatment with sepiapterin 7.5 mg/kg/day in participants 0 to < 6 months of age, 15 mg/kg/day in participants 6 to < 12 months of age, 30 mg/kg/day in participants 12 months to < 2 years of age, or 60 mg/kg/day in participants ≥ 2 years of age. Interim data indicate that daily sepiapterin administration is associated with an approximately 2.3-fold increase in mean daily Phe consumption (27.6 mg/kg/day at baseline versus 62.5 mg/kg/day at Week 26) while maintaining Phe levels < 360 μmol/L. The majority of subjects reached at least a 15% (76.7% of participants) or 30% (67.4% of participants) reduction in blood Phe (Figure 1).

Figure 1: Mean (SD) dietary Phe consumption over time during dietary Phe tolerance assessment (dietary Phe tolerance analysis set)



Phe, phenylalanine; PKU, phenylketonuria; RDA, recommended daily allowance; SD, standard deviation; W, week
Note: Baseline is defined as the average of daily dietary Phe consumption (mg/kg/day) at Month 1. The RDA is 0.8 g protein/kg, which is equivalent to approximately 40 mg/kg/day of Phe. Blood Phe levels baseline is the mean of the pre-assessment period Week 1–2. 1 g of protein is equivalent to approximately 50 mg of Phe.

These data indicate that sepiapterin treatment may allow liberalisation of the highly restrictive diet that patients with PKU must adhere to.

Subjects with history of allergies or adverse reactions to synthetic BH4 were excluded from the clinical studies.

The European Medicines Agency has deferred the obligation to submit the results of studies with Sephience in one or more subsets of the paediatric population in HPA (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following oral administration, sepiapterin is quickly absorbed, and the peak plasma concentrations occur in approximately 1 to 3 hours and decline to below the limit of quantitation (0.75 ng/mL) rapidly (generally by 12 hours). Maximum plasma sepiapterin concentration (C_{max}) was approximately 2.80 ng/mL following the 60 mg/kg/day dose for 7 days with a high-fat high-calorie diet. No accumulation of sepiapterin was observed following repeated dosing.

Plasma sepiapterin is metabolised extensively to form the pharmacologically active metabolite BH4. The apparent terminal half-life for BH4 is approximately 5 hours. Both BH4 C_{max} and area under the concentration-time curve from time zero to 24 hours postdose (AUC_{0-24h}) increased with the dose, while the increase was less than dose proportional when the sepiapterin dose was above 20 mg/kg. There is no accumulation of BH4 following repeated doses of sepiapterin up to 60 mg/kg for 7 days.

Effect of food
When sepiapterin was administered with a low-fat, low-calorie meal in the dose range of 20 to 60 mg/kg, BH4 exposures were 1.69- to 1.72-fold higher for C_{max} and 1.62- to 1.73-fold higher for AUC_{0-24h} compared to administration under fasted conditions. When sepiapterin was administered with a high-fat, high-calorie meal, BH4 exposures were 2.21- to 2.26-fold higher for C_{max} and 2.51- to 2.84-fold higher for AUC_{0-24h} compared to administration under fasted conditions.

Sepiapterin can be taken with any meal at any time of the day at the same time every day.

Distribution

Binding of sepiapterin or BH4 to plasma protein is low, and the majority of sepiapterin and BH4 in plasma are free to exert pharmacological effects. *In vitro* studies show that sepiapterin is bound (mean 15.4%) to plasma protein in the presence of 0.1% dithiothreitol in the concentration range of 0.1 to 10 μM. BH4 was 41.3% (at 2 μM), 33.0% (at 5 μM), and 24.1% (at 15 μM) bound to protein in human plasma in the presence of 0.5% β-mercaptoethanol.

In healthy subjects, elevated BH4 concentration was observed in the cerebrospinal fluid following repeated sepiapterin oral administration.

Biotransformation

Sepiapterin is metabolised by SR/carbonyl reductase and DHFR in a 2-step unidirectional process to form BH4. The metabolism of BH4 is presumed to follow the same pathway as endogenous BH4, oxidised while acting as coenzymes for aromatic amino acid hydroxylases, such as PAH, tyrosine hydroxylase, tryptophan hydroxylase, and alkylglycerol monooxygenase, and nitric oxide synthase, and some metabolites, like 4α-hydroxy-tetrahydrobiopterin and quinonoid dihydrobiopterin, could be recycled to regenerate BH4 mediated by pterin-4α-carbinolamine dehydratase and dihydropteridine reductase.

Extensive metabolism of sepiapterin was observed in human following a single oral dose of ^{14}C-sepiapterin. The major metabolic pathway involved oxidation/dehydrogenation,

reduction/oxidation, oxidative deamination, dehydration, side chain cleavage, and methylation, etc, alone or in combination.

Elimination

Following oral administration in healthy human participants, sepiapterin was extensively metabolised with the metabolites excreted primarily in faeces. Plasma sepiapterin declined rapidly following C_{max} to below the limit of quantitation, generally by 12 hours post-dose. Plasma BH4 declined mono-exponentially following C_{max}. The terminal half-life was approximately 5 hours.

Following a single oral dose of ^{14}C-sepiapterin to adult healthy subjects, a mean of 6.71% dosed radioactivity was recovered in urine and 26.18% in faeces with the combined total recovery of 32.9% by 240 hours. The majority of those radioactivity was recovered within the first 48 hours post-dose (28.2%). The total renal clearance of radioactivity derived from ^{14}C-sepiapterin was 1.54 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.

Special populations

Age
PKU patients of all ages had been included in the Phase 3 clinical studies. Except for allometric effect on clearance and volume of distribution, no further age effect was identified in the population PK study.

Ethnicity and race
Higher exposures to BH4 were observed for Asian subjects. In the Japanese ethno-bridging study, 10% to 24% higher $AUC_{0\text{-last}}$ and 14% to 29% higher C_{max} of BH4 were observed in Japanese compared to non-Japanese subjects at sepiapterin dose range of 20 to 60 mg/kg.

Renal impairment
The PK and safety of sepiapterin have not been studied in patients with renal impairment.

Hepatic impairment
The PK and safety of sepiapterin have not been studied in patients with hepatic impairment.

Drug interactions

In vitro studies
In vitro studies indicate that sepiapterin and BH4 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.

In vivo studies
In healthy subjects, co-administration of sepiapterin (20 mg/kg) with a single dose of the breast cancer resistance protein (BCRP) inhibitor curcumin (2 g) increased the exposures of BH4 slightly. The overall estimated geometric mean ratios (GMRs) (90% CI) for BH4 Cmax and area under the concentration-time curve from time zero to time of the last quantifiable measurement ($AUC_{0\text{-last}}$) when sepiapterin was co-administered with curcumin compared to sepiapterin alone were 1.24 (1.15-1.33) and 1.20 (1.13 1.28), respectively. This modest increase is deemed not clinically relevant.

Co-administration of a single dose of sepiapterin at the maximum therapeutic dose of 60 mg/kg with the BCRP substrate rosuvastatin (10 mg) had no effect on the of rosuvastatin. The overall estimated GMRs (90% CI) for rosuvastatin C_{max} and $AUC_{0\text{-last}}$ when rosuvastatin was co-administered with sepiapterin compared to rosuvastatin alone were 1.13 (1.00-1.28) and 1.02 (0.93-1.13), respectively.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

In rats, following repeated oral administration, sepiapterin-related renal tubule degeneration/regeneration, interstitial inflammation, and fibrosis were noted as a result of crystal deposition in the papillary collecting tubules. These findings were partially reversible after a 4-week recovery period and no kidney toxicity occurred at BH4 exposure levels 2 times the clinical BH4 exposure levels at the maximum recommended human dose (MRHD).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose (E460)
Isomalt (E953)
Mannitol (E421)
Croscarmellose sodium (E468)
Xanthan gum (E415)
Silica colloidal anhydrous or colloidal silicon dioxide (E551)
Sucralose (E955)
Magnesium stearate (E470)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

<u>After reconstitution</u>

Each dose should be administered immediately after reconstitution. The reconstituted solution should be discarded if not used within 24 hours when stored in a refrigerator (2 °C - 8 °C) or within 6 hours below 25 °C.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

Store in the original package in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Heat-sealed laminated aluminium foil sachet:
Polyethylene terephthalate, white extruded polyethylene (polyester/foil bond), aluminium foil (moisture barrier), and heat-sealed ionomeric resin (adhesive).

Each carton contains 30 unit-dose sachets.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed in accordance with local requirements.

Instructions for administration via enteral feeding tube

1) Ensure that the enteral feeding tube (size 6 Fr or 8 Fr) is free from obstruction before administration.
2) Flush the enteral feeding tube with 10 mL of water.
3) Administer the required dose of Sephience oral powder within 30 minutes of mixing (see section 4.2).
4) Flush the enteral feeding tube with at least 5 mL (6 Fr tube) or 15 mL (8 Fr tube) of water and administer the flush.

This medicinal product is compatible for use with silicone and polyurethane enteral feeding tube.

7. MARKETING AUTHORISATION HOLDER

PTC Therapeutics International Limited
Unit 1, 52-55 Sir John Rogerson's Quay
Dublin 2, D02 NA07
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1939/001
EU/1/25/1939/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

PTC Therapeutics International Limited
Unit 1, 52-55 Sir John Rogerson's Quay
Dublin 2, D02 NA07
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELING AND PACKAGE LEAFLET

A. LABELING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX

1. NAME OF THE MEDICINAL PRODUCT

Sephience 250 mg oral powder in sachet
sepiapterin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains 250 mg of sepiapterin.

3. LIST OF EXCIPIENTS

Contains isomalt (E953). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral powder
30 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Administer each dose immediately after reconstitution. Discard the mixture if not used within 24 hours when refrigerated (2 °C - 8 °C) or within 6 hours if stored below 25 °C.

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PTC Therapeutics International Limited
Unit 1, 52-55 Sir John Rogerson's Quay
Dublin 2, D02 NA07
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1939/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sephience 250 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

ALUMINIUM SACHET

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Sephience 250 mg oral powder in sachet
sepiapterin
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

250 mg

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton box

1. NAME OF THE MEDICINAL PRODUCT

Sephience 1 000 mg oral powder in sachet
sepiapterin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains 1 000 mg of sepiapterin.

3. LIST OF EXCIPIENTS

Contains isomalt (E953). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral powder
30 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Administer each dose immediately after constitution. Discard the mixture if not used within 24 hours when refrigerated (2 °C - 8 °C) or within 6 hours if stored below 25 °C.

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PTC Therapeutics International Limited
Unit 1, 52-55 Sir John Rogerson's Quay
Dublin 2, D02 NA07
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1939/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sephience 1 000 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Aluminium sachet

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Sephience 1 000 mg oral powder in sachet
sepiapterin
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 000 mg

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Sephience 250 mg oral powder in sachet
Sephience 1 000 mg oral powder in sachet
sepiapterin

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Sephience is and what it is used for

Sephience contains the active substance sepiapterin, which is a manmade version of a naturally occurring substance required to produce co-factor BH4. This is needed by certain enzymes (proteins) in the body to break down the amino acid Phe into tyrosine.

Sephience is used to treat hyperphenylalaninaemia (high blood levels of Phe) in patients of all ages with phenylketonuria (PKU). Our bodies break down the protein in foods into amino acids. PKU is an inherited disease where people cannot break down the amino acid Phe, causing it to build up in the blood and brain, which can be harmful.

Sepiapterin helps the body break down Phe, which allows it to reduce the harmful excess of phenylalanine in the blood.

2. What you need to know before you take Sephience

Do not take Sephience
- if you are allergic to sepiapterin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before taking Sephience.

When you are treated with Sephience, your doctor or nurse will test your blood regularly to check your Phe levels.

Long-term safety data in patients with PKU are limited (see section 4 for side effects evaluated to date for Sephience).

Other medicines and Sephience
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines. **In particular**, you should tell your doctor if you are using some medicines called 'dihydrofolate inhibitors (DHFR) inhibitors' that include antibiotics, immunosuppressants and medicines used to treat cancer (e.g. trimethoprim, methotrexate, pemetrexed, pralatrexate, and trimetrexate), medicines that cause dilation of blood vessels (such as glyceryl trinitrate (GTN), isosorbide dinitrate (ISDN), sodium nitroprusside (SNP), molsidomin, minoxidil), or levodopa (used to treat Parkinson's disease). Using these medicines may require more frequent monitoring of your blood.

Pregnancy, breast-feeding, and fertility
If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before taking this medicine. As a precaution it is preferable to avoid use of sepiapterin if you are pregnant or breast-feeding.

Sephience is not expected to affect fertility.

Driving and using machines
Sephience is not expected to affect the ability to drive and use machines.

Sephience contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per sachet, that is to say essentially 'sodium-free'.

Sephience contains isomalt (E953)
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Sephience

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Sephience is available as a powder that is dissolved in liquid, such as water or apple juice, or other soft food, and the mixture is then taken by mouth. The medicine can also be given through an enteral feeding tube.

How much Sephience to take
The dose, which depends on your age and weight in kilograms (kg), will be calculated by your doctor who prescribes it for you (or your child). Based on that calculated dose, your doctor will indicate to you how many sachets you should take daily.

The recommended dose is:

Children younger than 2 years
- Under 6 months of age: 7.5 mg/kg body weight once a day
- Between 6 and 12 months of age: 15 mg/kg body weight once a day
- Between 12 and 24 months of age: 30 mg/kg body weight once a day

Adults and children over 2 years of age
The recommended dose is 60 mg/kg body weight once a day.

How Sephience is taken
Sephience can be mixed in water, apple juice, or soft foods such as apple sauce or jams. The dose is based on age and body weight. Your doctor will tell you:
- Which sachet dose to use (250 mg or 1 000 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
- If necessary, Sephience may be administered via enteral feeding tube. For details how to do so, please ask your doctor, pharmacist or nurse.

There are 4 dosing groups based on age and weight.

1. For infants aged less than 12 months and weighing 16 kg or less (see Table 1)

- Take this medicine exactly as your doctor has told you according to your prescribed dose.
- **One** sachet will be used for patients in this dosing group.
- Before opening the Sephience oral powder sachet, shake or tap it on a hard surface to make sure the powder is at the bottom.
- Open the sachet of Sephience oral powder by carefully tearing or cutting the top of the sachet.
- Mix **one** 250 mg sachet in **9 mL** of water or apple juice.
- Mix well for 30 seconds or more until the mixture has no lumps.
- Once mixed, the mixture should be given immediately; if not, the mixture may be stored up to 24 hours in a refrigerator (2 °C - 8 °C) or for 6 hours when stored below 25 °C.
- If not given immediately, the mixture should be mixed again, just prior administration, for at least 30 seconds or more until the mixture has no lumps.
- Give the required dose (see Table 1) into the mouth using a syringe or into the enteral feeding tube.
- Rinse the syringe with extra water or apple juice (at least 15 mL) and swallow to make sure a full dose is taken.

Table 1: How to calculate the dose for children under 12 months of age by body weight

Weight (kg)	Dose: 7.5 mg/kg/day		Dose: 15 mg/kg/day	
	Age: 0 to less than 6 months		Age: 6 months to less than 12 months	
	Number of 250 mg sachets to be used	Volume to give (mL)	Number of 250 mg sachets to be used	Volume to give (mL)
2	1	0.6	1	1.2
3	1	0.9	1	1.8
4	1	1.2	1	2.4
5	1	1.5	1	3
6	1	1.8	1	3.6
7	1	2.1	1	4.2
8	1	2.4	1	4.8
9	1	2.7	1	5.4
10	1	3	1	6
11	1	3.3	1	6.6
12	1	3.6	1	7.2
13	1	3.9	1	7.8
14	1	4.2	1	8.4
15	1	4.5	1	9
16	1	4.8	1	9.6

2. For children aged 12 months to less than 2 years and weighing 16 kg or less (see Table 2)

- Take this medicine exactly as your doctor has told you according to your prescribed dose.
- Before opening the Sephience oral powder sachet(s), shake or tap it on a hard surface to make sure the powder is at the bottom.
- Open the sachet(s) of Sephience oral powder by carefully tearing or cutting the top of the sachet.
- Mix each 250 mg sachet (see Table 2) with **9 mL** of water or apple juice. When more than one sachet is recommended, the sachets can be mixed together with the corresponding amount of water or apple juice (e.g. two 250 mg sachets mixed with 18 mL of water or apple juice).
- Mix well for at least 30 seconds or more until the mixture has no lumps.

- Once mixed, the dose should be given immediately; if not, the mixture may be stored for up to 24 hours in a refrigerator (2 °C - 8 °C) or for 6 hours when stored below 25 °C.
- If not taken immediately, the mixture should be mixed again, just prior administration, for at least 30 seconds or more until the mixture has no lumps.
- Give the required dose (see Table 2) into the mouth using a syringe or into the enteral feeding tube.
- Rinse the syringe with extra water or apple juice (at least 15 mL) and swallow to make sure a full dose is taken.

Table 2: How to calculate the dose for children aged 12 months to less than 2 years of age by body weight

Weight (kg)	**Dose: 30 mg/kg/day**	
	Age: 12 months to less than 2 years	
	Number of 250 mg sachets	**Volume to give (mL)**
2	1	2.4
3	1	3.6
4	1	4.8
5	1	6
6	1	7.2
7	1	8.4
8	1	9.6
9	2	10.8
10	2	12
11	2	13.2
12	2	14.4
13	2	15.6
14	2	16.8
15	2	18
16	2	19.2

3. For children aged over 2 years and weighing 16 kg or less (see Table 3)

- Take this medicine exactly as your doctor has told you according to your prescribed dose.
- Before opening the Sephience oral powder sachet(s), shake or tap it on a hard surface to make sure the powder is at the bottom.
- Open the sachet(s) of Sephience oral powder by carefully tearing/or cutting the top of the sachet.
- Mix each 250 mg sachet (see Table 3) with **9 mL** of water or apple juice. The sachets can be mixed together with the corresponding amount of water or apple juice (e.g. two 250 mg sachets mixed with 18 mL of water or apple juice).
- Mix well for at least 30 seconds or more until the mixture has no lumps.
- Once mixed, the dose should be given immediately; if not, the mixture may be stored for up to 24 hours in a refrigerator (2 °C - 8 °C) or within 6 hours when stored below 25 °C.
- If not taken immediately, the mixture should be mixed again, just prior administration, for at least 30 seconds or more until the mixture has no lumps.
- Give the required dose (see Table 3) into the mouth using a syringe, or into the enteral feeding tube.
- Rinse the syringe with extra water or apple juice (at least 15 mL) and swallow to make sure a full dose is taken.

Table 3: How to calculate the dose for patients over 2 years of age weighing 16 kg or less

Weight (kg)	**Dose: 60 mg/kg/day**	
	Age: 2 years and older	
	Number of 250 mg sachets	**Volume to give (mL)**
5	2	12

6	2	14.4
7	2	16.8
8	2	19.2
9	3	21.6
10	3	24
11	3	26.4
12	3	28.8
13	4*	31.2
14	4*	33.6
15	4*	36
16	4*	38.4

* Instead of the four 250 mg sachets, one full 1 000 mg sachet can be mixed with 36 mL of water or apple juice. This mixture should be administered with a syringe, according with the volume detailed on Table 3.

4. For patients 2 years or older and weighing 16 kg or more (see Table 4)

- Take this medicine exactly as your doctor has told you according to your prescribed dose.
- Before opening the Sephience oral powder sachet(s), shake or tap it on a hard surface to make sure the powder is at the bottom.
- Open the sachet(s) of Sephience oral powder by carefully tearing/or cutting the top of the sachet.
- Mix each sachet (see Table 4) with water or apple juice (9 mL for each 250 mg sachet; 20 mL for each 1 000 mg sachet) or 2 tablespoons of apple sauce or jam. When more than one sachet is recommended, the sachets can be mixed together with the corresponding amount of water or apple juice (e.g. one 250 mg sachet mixed with 9 mL of water or apple juice and one 1 000 mg sachet mixed with 20 mL of water or apple juice).
- If using water or apple juice, mix well for at least 30 seconds or more until the mixture has no lumps.
- If using apple sauce or jam, mix well for at least 60 seconds or more until the mixture has no lumps.
- Once mixed, the dose should be given immediately; if not, the mixture may be stored for up to 24 hours in a refrigerator (2 °C - 8 °C) or within 6 hours when stored below 25 °C.
- If not taken immediately, the mixture should be mixed again, just prior administration, for at least 30 seconds or 60 seconds as above.
- Drink or give the required dose (see Table 4) into the mouth using a glass or plastic cup, or give the required dose into the enteral feeding tube.
- Rinse the container with extra water or apple juice (at least 15 mL) and swallow to make sure a full dose is taken.

Table 4: How to calculate the volume needed for the dose for patients 2 years and older and weighing 16 kg or more

Number of 250 mg sachets	Number of 1 000 mg sachets	Volume of water or apple juice to add (mL)
0	1	20
1	1	29
2	1	38
3	1	47
0	2	40
1	2	49
2	2	58
3	2	67
0	3	60

1	3	69
2	3	78
3	3	87
0	4	80
1	4	89
2	4	98
3	4	107
0	5	100
1	5	109
2	5	118
3	5	127
0	6	120

If you forget to take Sephience
If you forget to take the dose at the right time, take it as soon as you remember on the same day, or on the next day as normal.

Do not take a double dose to make up for a forgotten dose.

If you stop taking Sephience
Do not stop taking Sephience without prior discussion with your doctor, as phenylalanine levels in your blood may increase.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common side effects (may affect more than 1 in 10 people)
- Upper respiratory (nose and throat) infection
- Headache
- Diarrhoea
- Abdominal (belly) pain

Common side effects (may affect up to 1 in 10 people)
- Unusually coloured stools
- Low levels of phenylalanine (an essential amino acid) in the blood

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Sephience

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the sachet and the carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special temperature storage conditions.

Store in the original package in order to protect from light.

After mixing the medicine, take it immediately. If not, the mixture may be stored up to 24 hours in a refrigerator (2 °C - 8 °C) or within 6 hours below 25 °C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Sephience contains

- The active substance is sepiapterin. Each sachet contains 250 mg or 1 000 mg of sepiapterin.
- The other ingredients are microcrystalline cellulose (E460), isomalt (E953), mannitol (E421), croscarmellose sodium (E468), xanthan gum (E415), silica colloidal anhydrous or colloidal silicon dioxide (E551), sucralose (E955), and magnesium stearate (E470). See section 2 for further information on isomalt (E953) and sodium.

What Sephience looks like and contents of the pack

The oral powder is yellow to orange in colour.
The powder is filled in single-use sachets containing 250 mg or 1 000 mg of sepiapterin.

Sephience is available in cartons containing 30 sachets of 250 mg or 1 000 mg.

Marketing Authorisation Holder and Manufacturer

PTC Therapeutics International Limited
Unit 1, 52-55 Sir John Rogerson's Quay
Dublin 2, D02 NA07
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

AT, BE, BG, CY, CZ, DK, DE, EE, EL, ES, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SI, SK, FI, SE
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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website: https://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.