swissmedic

Date: 14 October 2025
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Sephience

International non-proprietary name:	sepiapterin
Pharmaceutical form:	oral powder
Dosage strength(s):	1000 mg, 250 mg
Route(s) of administration:	oral
Marketing authorisation holder:	PTC Therapeutics Switzerland GmbH
Marketing authorisation no.:	69810
Decision and decision date:	approved on 5 August 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, definitions, abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BH4	Tetrahydrobiopterin
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
COX1	Cyclooxygenase-1
CSF	Cerebrospinal fluid
CYP	Cytochrome P450
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GABA	Gamma-aminobutyric acid
GI	Gastrointestinal
GLP	Good Laboratory Practice
hERG	Human ether-à-go-go-related gene
HPLC	High-performance liquid chromatography
HPLC-MS/MS	High-performance liquid chromatography coupled with tandem mass spectrometry
HPA	Hyperphenylalaninemia
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ikr	Rapid delayed rectifier potassium current
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
Lck	Lymphocyte-specific protein tyrosine kinase
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
Phe	Amino acid phenylalanine
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PKU	Phenylketonuria
PND	Postnatal day
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan

SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

New active substance status
The applicant requested new active substance status for sepiapterin in the above-mentioned medicinal product.

Fast-track authorisation procedure
The applicant requested a fast-track authorisation procedure in accordance with Article 7 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA. Orphan drug status was granted on 14 May 2024.

2.2 Indication and dosage

2.2.1 Requested indication

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

2.2.2 Approved indication

Treatment of hyperphenylalaninemia (HPA) in adult and paediatric patients with phenylketonuria (PKU) who have been shown to be responsive to such treatment.

2.2.3 Requested dosage

Summary of the requested standard dosage:

Sephience is administered orally once daily with food using a mg/kg dosage. Sephience oral powder is available in individual sachets of 250 or 1000 mg and should be mixed into water, apple juice or a small amount of a soft food such as apple purée or jam.

The recommended dosage of Sephience in patients aged ≥ 2 years is 60 mg/kg/day. The maximum recommended dosage is 60 mg/kg/day.

2.2.4 Approved dosage

(See appendix)

2.3 Regulatory history (milestones)

Application	8 July 2024
Formal control completed	9 July 2024
List of Questions (LoQ)	30 August 2024

Response to LoQ	30 December 2024
Second List of Questions (2. LoQ)	18 February 2025
Response to 2. LoQ	11 May 2025
Preliminary decision	27 June 2025
Response to preliminary decision	16 July 2025
Final decision	5 August.2025
Decision	approval

3 Medical context

Phenylketonuria (PKU) is a rare autosomal recessive metabolic disorder caused by mutations in the gene encoding phenylalanine hydroxylase (PAH), an enzyme responsible for converting the amino acid phenylalanine (Phe) into tyrosine, a precursor for many neurotransmitters. PAH requires tetrahydrobiopterin (BH4) as a cofactor to function. In PKU, a PAH deficiency or dysfunction leads to an accumulation of Phe in the blood and brain. Elevated Phe levels are neurotoxic and, if untreated, can result in severe intellectual disability, developmental delays, behavioural problems, and other neurological complications. The severity of PKU varies depending on PAH residual activity, with classical PKU being the most severe form. Early diagnosis and management are critical to preventing irreversible damage, particularly in newborns and young children.
PKU is a rare condition, with an estimated global incidence of 1 in 10,000 to 15,000 live births, though prevalence varies by region and ethnicity. Newborn screening programmes have significantly improved early detection rates, allowing for timely intervention. Advances in genetic testing have also made it possible to identify carriers and make a prenatal diagnosis in families with a history of PKU.

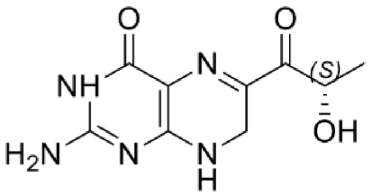
The cornerstone of PKU management is a lifelong low-phenylalanine diet, which involves restricting natural protein intake and supplementing with medical foods or amino acid-based formulas to ensure adequate nutrition. This dietary approach aims to maintain blood Phe levels within a safe range, typically below 360 µmol/L in patients ≤ 12 years and women before and during pregnancy, and below 600 µmol/L in patients > 12 years of age, as recommended by European guidelines. However, adherence to this diet can be challenging, particularly for adolescents and adults, due to its restrictive nature and impact on quality of life.
Pharmacological treatments have been developed to complement dietary management. Sapropterin (Kuvan), a synthetic form of BH4, is approved for use in patients with BH4-responsive PKU. It works by enhancing residual PAH activity, thereby reducing blood Phe levels. However, not all patients respond to sapropterin. Pegvaliase, an enzyme substitution therapy, is another option for adolescents aged 16 and over with PKU who have not achieved adequate Phe control with other treatments. While approved in the EU, it is not, however, authorised in Switzerland, and is associated with a higher risk of adverse effects, including allergic reactions.

The new chemical entity sepiapterin is a precursor molecule of BH4 and is therefore close to the approved substance sapropterin. It is assumed that in addition to the chaperone effect of BH4, sepiapterine has an independent chaperone effect on PAH and is actively transported into the cell, reaching higher concentrations there compared to sapropterin. This dual mechanism of action may allow a broader range of PKU patients to benefit from sepiapterin, including those who are nonresponsive to sapropterin. Sepiapterin could provide an additional treatment option for PKU, particularly for patients with a limited response to existing therapies. However, dietary management would still be necessary to optimise outcomes.

4 Quality aspects

4.1 Drug substance

INN: sepiapterin
Chemical name: 2-amino-6-[(2S)-2-hydroxypropanoyl]-7,8-dihydro-3H-pteridin-4-one
Molecular formula: $C_9H_{11}N_5O_3$
Molecular mass: 237.22 g/mol
Molecular structure:



Sepiapterin drug substance is a yellow to orange powder with a melting point of 223.3°C. It shows polymorphism; the form known to be most stable in the solid state was chosen. Sepiapterin is slightly soluble in water over the physiological pH range and is moderately hygroscopic. It has one chiral centre and is manufactured as the enantiomerically pure S-enantiomer.

The drug substance is obtained by a synthetic route involving several chemical steps, including deprotection of protective groups, reduction and oxidation steps. The final drug substance in its desired polymorphic form is isolated and purified by crystallisation. The process includes several intermediates.

In order to ensure a consistent quality of the drug substance precursor, the specifications include all relevant test parameters as recommended by the relevant ICH guidelines and are compliant with current Ph. Eur. The analytical methods are adequately described and the non-compendial methods are fully validated in accordance with ICH guidelines.

Appropriate stability data have been generated, resulting in a suitable retest period.

4.2 Drug product

Sephience Oral Powder is an immediate-release solid dosage form available in 250 and 1000 mg dosage strengths and packaged in sachets.

The manufacturing process yields an appropriate quality.

Appropriate specifications have been defined, and analytical procedures have been validated. Appropriate stability data have been generated in the packaging material intended for commercial use.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

5.1 Pharmacology

Sepiapterin is an endogenous naturally occurring precursor of tetrahydrobiopterin (BH4) and is metabolised to form BH4 via the pterin salvage pathway. The applicant provided one in vitro and two in vivo studies to confirm the proposed mode of action. COS-7 cells were transiently transfected with plasmid vectors carrying a plethora of phenylalanine hydroxylase (PAH) mutations. Incubation with 5 or 20 µM sepiapterin for 48 hours resulted in increased PAH activity when normalised to wild-type transfected non-treated cells of 19 out of 62 variants in total, but of 10 of the 15 most common PAH protein variants. Furthermore, sepiapterin and BH4 stabilised the mutant protein, indicating chaperone activity. An in vivo investigation in male mice after a single oral dose of sepiapterin or BH4 demonstrated good tolerance. The data showed a higher increase in BH4 concentration in the liver and kidneys after sepiapterin treatment than after BH4 treatment. The actual decrease in phenylalanine was not demonstrated. However, this is acceptable from the nonclinical point of view.

Secondary pharmacodynamics studies using 10 µM sepiapterin across 94 off-targets showed no significant inhibition or stimulation. Moderate inhibition was observed for glycine, GABA transporter, COX1, and Lck, but a clinical Cmax of 1.45 µM suggests a low risk of adverse effects.

As regards safety pharmacology, the applicant provided stand-alone in vitro studies for the cardiovascular system and included relevant endpoints for the respiratory or central nervous system into the repeat-dose toxicity studies. Neither sepiapterin nor BH4 inhibited the IKr in the hERG assay at concentrations of 30 or 866 µM. The rat and monkey toxicity studies did not identify any concerns with regard to the cardiovascular, central nervous or respiratory systems, with safety margins between 2 (rats) and 8 (monkey). Clinical data confirmed the overall good safety profile.

No nonclinical PD drug interaction studies have been conducted.

5.2 Pharmacokinetics

The applicant submitted reports of validated HPLC-MS/MS methods to determine sepiapterin and BH4 concentrations in plasma from mice, rats, and marmoset monkeys in toxicity studies.

Different formulations tested in single-dose studies in male mice, rats, dogs, and monkeys with oral administration had no significant impact on the pharmacokinetic profile. In general, sepiapterin quickly converted to BH4, with peak plasma BH4 concentration observed around 2.5 to 3 hours post-dose. In repeat-dose studies, BH4 displayed non-linear kinetics, with a less than dose-proportional increase due to possible rate-limiting conversion, absorption saturation, or induced elimination. Monkeys and rats showed similar exposure to sepiapterin and BH4 across sexes and doses.

Sepiapterin showed low human plasma protein binding (84.6% unbound fraction), while BH4 binding in human plasma ranged from 41.3% to 24.1%, depending on the sepiapterin concentration. The applicant did not provide any animal plasma protein binding data, but comparable levels are expected. In rats, 14C-sepiapterin showed widespread tissue distribution, peaking at 4-8 hours post-dose, with the highest concentrations in the endocrine (adrenals, pituitary and thyroid glands), metabolic/excretory systems, and the tissues of the gastrointestinal tract. Though there was measurable distribution to the central nervous system, the concentrations were lower than in most other tissue systems and negligible after 48 h. Distribution of radioactivity to certain melanin-containing tissues was low without extended retention, indicating no melanin binding.

Sepiapterin metabolism is primarily mediated by sepiapterin reductase, probably assisted by carbonyl reductase and dihydrofolate reductase in a unidirectional 2-step reduction to form BH4 within the pterin salvage pathway. The applicant did not provide in vitro studies, but in vivo studies in rats and monkeys showed that unchanged sepiapterin was a minor component in plasma, and that BH4

adducts/artifacts were more prevalent. No unique human metabolites were identified. Sepiapterin and BH4 were primarily excreted via faeces in rats and monkeys (84.7% and 89.3%), with minor urinary excretion (9.2% and 8.6%). Similar excretion patterns were observed in humans. No milk excretion studies were conducted.

5.3 Toxicology

Rats and marmoset monkeys were considered relevant species due to their pharmacological response (i.e., increase in BH4) and pharmacokinetic profile. The applicant conducted repeat-dose toxicity studies in rats and monkeys for up to 26 and 39 weeks using daily oral administration, as intended in the clinical setting.

Both species showed discoloured faeces and/or fur due to sepiapterin and its metabolites. In the rat studies, the kidneys were identified as a potential target organ, showing increased weight, tubular degeneration, crystals, inflammation, and fibrosis at higher doses. These findings were at least partially reversible. In the liver, minimal to mild hepatocellular vacuolisation was noted in high-dose animals in the 26-week rat study. No such findings were recorded in monkeys. Safety margins ranged from 2 to 8 (based on AUC) in the long-term studies.

Sepiapterin did not induce mutations in five bacterial strains at concentrations up to 5000 µg/plate. In an in vitro study with human lymphocytes, the compound was clastogenic. In vivo studies in male rats with adequate exposure showed no micronuclei formation at doses up to 2000 mg/kg and no biologically relevant DNA damage. Overall, sepiapterin is considered non-genotoxic. The applicant addressed the carcinogenic risk with a comprehensive assessment. This indicated a low carcinogenic risk. A 26-week study with transgenic mice involving doses of up to 1000 mg/kg did not identify any effects on survival or carcinogenic effects.

The applicant conducted reproductive and developmental toxicity studies in line with ICH S5(R3). No adverse effects on mating and fertility were observed in rats treated with up to 300 mg/kg daily. In the embryofetal developmental toxicity studies in rats and rabbits, doses of up to 1000 mg/kg sepiapterin did not cause any malformations or embryofetal death. In the pre- and postnatal development study, no adverse effects were observed in rats treated with up to 300 mg/kg from gestation day 6 through postpartum day 20 or in the F1 generation in terms of survival, clinical signs, body weight, or developmental milestones. The safety margins based on AUC ranged from 6 to 9.

As regards juvenile toxicity, a 6-day study in rats (postnatal day (PND) 4 to 9) showed dose-dependent increases in BH4 concentrations. A 10-week study (PND 4 to PND 70) with doses up to 300 mg/kg yielded no relevant concerns regarding sexual maturation, sperm evaluation, behavioural parameters, or femur measurements. The safety margin based on AUC was 4.

The Paediatric Investigation Plan did not include any nonclinical measures.

Sepiapterin was not considered phototoxic on the basis of in vitro testing.

As regards the abuse potential, a weight of evidence assessment was provided and considered sufficient, raising no concerns.

There are no concerns with regard to the excipients in the drug product. The specified impurities were qualified by the general repeat-dose or dedicated qualification studies in rats.

Due to the nature of the drug, sepiapterin is unlikely to result in a significant risk to the environment.

The nonclinical safety specifications in the RMP adequately reflect in the findings in the nonclinical testing programme.

5.4 Nonclinical conclusions

Overall, the submitted nonclinical documentation is considered sufficient to support the approval of Sephience with the new active substance sepiapterin in the proposed indication. The pharmacological properties of sepiapterin were adequately characterised, as were its pharmacokinetic and toxicity profiles. All nonclinical data that are relevant for safety are included in the Information for healthcare professionals.

6 Clinical aspects

6.1 Clinical pharmacology

ADME

Sepiapterin and its active metabolite tetrahydrobiopterin (BH_4) are endogenous substances. Sepiapterin undergoes fast biotransformation through sepiapterin reductase and dihydrofolate reductase to BH_4. BH_4 baseline values ranged from approx. 3 ng/mL in healthy volunteers to approx. 6 ng/mL in PKU patients, whereas sepiapterin plasma levels were not quantifiable at baseline. At the highest tested dose of 60 mg/kg sepiapterin, BH_4 mean PK parameters at steady state were 343 ng/ml for C_{max}, 2462 ng*h/ml for AUC_{tau} and 14.9 ng/mL for C_{trough} based on the final PopPK model. Overall, sepiapterin plasma exposure is below 1% of the BH_4 exposure at steady state.

Absorption

Sepiapterin undergoes fast biotransformation to BH4, which is considered the active principle. After 8 hours, the majority of the PK samples for sepiapterin were below the level of quantification. Maximum BH_4 concentrations were measured around 5 h after dose administration, and no accumulation of BH_4 has been observed after multiple doses.

No absolute bioavailability study was conducted.

Food effect

Administration of a sepiapterin drug suspension of the market formulation with food caused an increase in exposure. Food appeared to have a dose-independent effect on bioavailability . Dosing instructions state that the drug product has to be taken with food, which was also the dosing instruction in the pivotal study.

Distribution

Sepiapterin and the active principle BH_4 show low plasma protein binding. Human plasma protein binding for sepiapterin was 15.4%.

The blood-to-plasma ratio of the total radioactivity in a human ADME study was 0.65, indicating that the total radioactivity in blood was associated more with plasma than with blood cells. Within plasma and blood, long lasting total radioactivity was found over the course of the study (up to 192 h post-dose), which contrasts with the rapid elimination of sepiapterin and BH_4. A mass-balance study found a dual exposure peak in plasma for total radioactivity, with the T_{max} of the primary peak around 5 h post-dose and a secondary peak 32h to 48 h post-dose. It is likely that sepiapterin and BH_4 are metabolised and recycled for biosynthesis, thus leading to secondary peaks in total radioactivity.

In cerebrospinal fluid (CSF), a 2-fold increase in BH_4 compared to baseline was observed in healthy volunteers who received the highest recommended dose of 60 mg/kg. The clinical implications of this finding are unknown, as this is much lower than plasma, where a more than 100-fold increase from baseline is reached.

Metabolism

The metabolism of sepiapterin was assessed in a human mass-balance study. The major metabolic pathways involved hydrogenation/reduction, dehydrogenation, oxidative deamination, dehydration, oxidation, methylation, C-C bond side chain cleavage alone, or a combination thereof.

Analysis of the plasma identified 11 metabolites, and sepiapterin was a minor circulating component. M181/1 (7,8-dihydroxanthopterin [XH_2]) and BH_4 were the most abundant metabolites, accounting for 16.4% and 9.2% of the total radioactivity, respectively.
Given the intrinsic instability of BH_4 and other reductive metabolites, the conversion into more stable biopterins is likely to have occurred during extensive sample processing.

Elimination

The terminal half-life of sepiapterin could not be determined, due to insufficiently dense PK sampling. The terminal half-life of BH_4 was approx. 4.5 h.

Within the mass-balance study, 32.9% of the radioactive dose was recovered in combined urine and faeces, with a mean of 6.7% in urine and a mean of 26.2% in faeces; most of the radioactivity was recovered within 48 hours post-dose. The overall low recovery is attributable to sepiapterin and BH_4 being endogenous molecules that are incorporated into salvage pathways. Furthermore, an *in vitro* incubation of sepiapterin with human intestinal microbiota under anaerobic conditions indicated the formation of volatile metabolite(s).

Special populations

Paediatric population of 2 years and older

Paediatric patients in the 2 to 18 age group were included in pivotal study PTC923-MD-003, and open label study PTC923-MD-004. The paediatric patient population between 2 and 18 years were adequately represented in clinical studies, accounting for more than 50% of the PKU population.

The PK of BH_4 is dependent on body weight, which justifies the BW-based dosing recommendation. In the latest PopPK model, bodyweight effects on volumes and clearances were accounted for by allometric scaling using standard fixed values. In addition, the effect of age as a continuous covariate was assessed on different model parameters, and was not found to be significant. However, bodyweight-adjusted dosing leads to over-adaptation of the dose, resulting in lower exposures at the same dose level for lower bodyweight. For example, a 14.2-kg patient would have 23% and 30% lower C_{max} and AUC than a 70-kg patient. This effect is not deemed clinically meaningful over the age range down to 2 years and a dose level of 60 mg/kg.

Paediatric population below 2 years

The dose prediction model used to select doses for paediatric patients was developed on the basis of PK data from adult healthy volunteers in the entry-into-human study. The model assumed a maturation function on BH_4 clearance, leading to a predicted lower clearance in patients below 2 years old. Thus, lower doses were selected for investigation in the paediatric population below 2 years of age in order to achieve an exposure similar to that observed in adults. At a later stage of development, it was found that exposure data from paediatric patients younger than 2 years did not support the maturation function. The latest PopPK model included PK data from 3 paediatric patients who were less than 1 year old, where the youngest included patient was 4.5 months old and 6 patients were between 1-2 years. The data support a dosing regimen of 60 mg/kg across all ages range for a comparable BH_4 exposure. Nevertheless, the initially selected dose levels were investigated for efficacy in the paediatric population (see Information for healthcare professionals).

Interactions

The interaction potential of sepiapterin and BH_4 have been sufficiently well characterised and the risk of clinically relevant interactions is low (see Information for healthcare professionals).

Pharmacodynamics

BH_4 is a cofactor for several aromatic amino acid hydroxylases including PAH. Mutant PAH with a residual activity may be activated with BH_4, thus leading to a reduction in phenylanine in the blood. Since the mutants can be multi-fold, and both residual activity and response to BH_4 differ between PKU patients, individual dose adaptation and initial responder analysis is indicated. This is further supported by the fast treatment response observed in phenylalanine concentrations.

In vitro, sepiapterin increases the activity of PAH mutant proteins to a similar extent as BH_4. *In vivo*, however, sepiapterin is rapidly converted to BH_4, and sepiapterin exposure is less than 1% of BH_4

exposure. Therefore, the relevance of sepiapterin functioning as an independent chaperone is unclear.

Secondary pharmacology

A dedicated TQT study was conducted by the applicant with dose levels of 60 mg/kg and 120 mg/kg in healthy volunteers. No effect on QTcF was observed.

Exposure-efficacy relationship

Exposure-response models were developed to assess the effect of BH_4 on Phe levels in PKU patients. Since sepiapterin exposure levels were generally less than 1% of BH_4 exposure, the efficacy-response model was only developed for BH_4 exposure levels derived from PopPK models.

The latest PopPK/PD model is an E_{max} turn-over model, where the elimination of Phe (k_{out}) is directly linked to the central BH_4 concentration. The model adequately describes the exposure-response relationship for phenylalanine concentrations in blood in PKU patients receiving sepiapterin. The model includes a covariate selecting responders vs non-responders based on the patient's initial treatment response. This supports a dosing regimen where sepiapterin susceptibility is tested at treatment initiation, since no specific patient characteristics that could be used to identify non-responders were found.

The conclusions of the exposure-response model reports support a dose of 60 mg/kg across all age groups for comparable response rates across all age ranges. For example, the calculated response rate as a percentage of PKU patients achieving Phe target concentrations below 360 µM is 62.1% in patients ≥ 2 years receiving 60 mg/kg, whereas the calculated response rate is 41.2% in patients below 6 months receiving 7.5 mg/kg.

In the final dataset, the applicant presented data from 32 patients below the age of 2 (24 patients between 1 and 2 years, and 8 patients below the age of 1), receiving the standard doses as displayed in the Information for healthcare professionals. Although a similar response rate was observed in this dataset compared to patients ≥ 2 years, it is highly likely that a higher percentage of paediatric PKU patients < 2 years would benefit from higher doses than the investigated dose levels. Thus, dose increments to up to 60 mg/kg in patients below 2 years are recommended at the discretion of the treating physician in cases where there is insufficient response at treatment initiation.

6.2 Dose finding and dose recommendation

In the open-label active-controlled dose-finding **study 002**, sepiapterin doses of 20 mg/kg/d and 60 mg/kg/d were compared to sapropterin 20 mg/kg/d over 7 days treatment in 24 PKU patients ≥ 18 years and ≤ 60 years of age. Under 60 mg/kg sepiapterin, the reduction of blood Phe levels was more pronounced compared to the 20 mg/kg sepiapterin group and the 20 mg/kg sapropterin group. The 20 mg/kg sepiapterin dose was more effective than 20 mg/kg sapropterin. For the pivotal trial, the 60 mg/kg sepiapterin dose was chosen as the target maintenance dose, although the 20 mg/kg dose also showed relevant effects.

6.3 Efficacy

Pivotal **study 003** had a 2-part, multi-centre, randomised, double-blind, placebo-controlled design. It included patients of any age with a clinical diagnosis of PKU, a current minimum Phe level of ≥360 µmol/L, and a medical history of at least 2 blood Phe measurements of ≥600 µmol/L.
Part 1 of this study identified responders to sepiapterin (≥ 30% decrease in blood Phe levels), who were then treated in part 2 of the study with escalating doses of sepiapterin at 2-week intervals (20 mg/kg daily for weeks 1 and 2, 40 mg/kg daily for weeks 3 and 4, and 60 mg/kg daily for weeks 5 and

6). Participants were required to continue their usual diet without modification. Around 2/3 of the initial part 1 population were transferred to part 2 as responders, patients <2 years of age were not included in the primary efficacy analysis.

At the primary endpoint “mean change in blood Phe levels from baseline to weeks 5 and 6 (average over a 2-week period)” in the part 2 double-blind phase, the uptitrated sepiapterin 60 mg/kg/d was associated with a statistically significant difference of approx. -400 µmol/L versus placebo. This outcome was supported by results at secondary endpoints, such as the effects in the full analysis set (including patients with a response of ≥ 15% and < 30% in part 1), responder analyses (≥ 30% decrease in blood Phe levels), and reaching age-appropriate target Phe blood concentrations. Furthermore, relevant treatment effects were also observed in several subgroups and age categories, as well as in patients with prior treatment nonresponse to sapropterin or patients with classical PKU (cPKU). A substantial decrease in the blood Phe concentration in part 2 of this study was already observed after week 2 of the uptitration period under 20 mg/kg/d sepiapterin. In view of these results, the lower doses of 20 mg/kg and 40 mg/kg should also be offered at the treating physician’s discretion.

In the ongoing open-label extension **study 004**, patients from study 003 received continued treatment with the 60 mg/kg/d dose, as well as lower doses of 7.5, 15 and 30 mg/kg according to different age categories for patients below 2 years of age. The main objectives were to assess safety and the changes from baseline in dietary phenylalanine consumption. The secondary objectives were quality of life parameters (not reported with the submitted interim report). Only patients whose blood Phe levels stayed <360 µmol/L were included in the dietary Phe tolerance analysis set. By the cut-off date for the currently available interim report, daily use of sepiapterin had led to an approx. 2.3-fold increase in mean daily Phe consumption in the dietary Phe tolerance analysis set. The improvement in dietary Phe tolerance in long-term treatment supports the beneficial effects observed in study 003.

Efficacy data for patients < 2 years of age were mainly derived from the study 004, where a relevant response of > 30% Phe blood level reduction was shown for the majority of the 32 participants.

For further details concerning efficacy, see the appendix of this report.

6.4 Safety

Sepiapterin in doses of up to 60 mg/kg/day was well tolerated. The overall safety profile appeared to be similar to that observed with the approved substance sapropterin, with mostly mild gastrointestinal adverse effects observed in the clinical studies. The pool of safety data for patients < 2 years of age is still limited, and additional data will be gathered from the ongoing long-term study 004 during the postmarketing phase.

For further details concerning safety, see the appendix of this report.

6.5 Final clinical benefit-risk assessment

Pivotal clinical study 003 showed that compared to placebo, 60 mg/kg/day sepiapterin had statistically significant and clinically relevant effects in lowering blood Phe levels in patients ≥ 2 years of age. Effects observed in phase 2 study 002 under 20 mg/kg/d and during the uptitration in study 003 under 20 mg/kg/d and 40 mg/kg/d showed that lower doses than the proposed standard dose for patients ≥ 2 years of age are also useful treatment options, since they offer greater flexibility in treatment combined with diet. The Information for healthcare professionals (HCPs) now includes this option for down-titration in patients ≥ 2 years of age on the basis of Phe blood levels. Extension study 004 has delivered supportive evidence for long-term efficacy and safety in an interim report based on Phe tolerance data.

Additional efficacy and safety data from study 004 were submitted with the responses to the LoQ, supporting efficacy and safety in patients < 2 years of age. However, the available PK data indicated that the proposed standard doses (7.5, 15, 30 mg/kg/d according to different age categories < 2 years of age) might be too low for at least some subjects. Therefore, additional higher doses up to 60 mg/kg were proposed by Swissmedic for patients < 2 years of age in the event of an inadequate response to the standard dose, and the Information for HCPs now includes such flexible dosing options.

The flexible dosing options are also considered to be adequate, firstly because treatment with sepiapterin will be started and supervised entirely by experts in specialised centres, and secondly because treatment response can easily be determined by means of blood Phe level measurements. Additionally, the safety profile of sepiapterin appeared to be comparable to that of the approved substance sapropterin and is generally considered as benign.

Based on these considerations, the balance of benefits versus risks of Sephience is considered as positive, and the application can be approved.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Sephience was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This enables rapid identification of new safety findings. Healthcare professionals are encouraged to report suspected new or serious adverse reactions. For information on reporting adverse reactions, see the "Adverse reactions" section.

SEPHIENCE™ 250 mg / 1000 mg ORAL POWDER IN SACHET

Composition

Active substances

Sepiapterin

Excipients

Cellulosum microcristallinum, isomaltum (E953), mannitolum (E421), carmellosum natricum conexum, xanthani gummi, silicium dioxydatum colloidalis, sucralosum, magnesii stearas

Each 250 mg sachet contains 400 mg isomaltum and maximum 0.9 mg sodium.

Each 1000 mg sachet contains 1600 mg isomaltum and maximum 3.6 mg sodium.

Pharmaceutical form and active substance quantity per unit

Sepiapterin 250 mg oral powder.
Each sachet contains 250 mg of sepiapterin.

Sepiapterin 1000 mg oral powder.
Each sachet contains 1000 mg of sepiapterin.

Indicationen/Uses

Sephience is indicated for the treatment of hyperphenylalaninemia (HPA) in adult and paediatric patients with phenylketonuria (PKU) who have been shown to be responsive to such treatment.

Dosage/Administration

Treatment with Sephience must be initiated and monitored by a physician experienced in the treatment of PKU. Sephience should be initiated in conjunction with a phenylalanine (Phe)-restricted diet.

All patients treated with Sephience should undergo regular clinical examinations to determine the appropriate diet in consultation with the treating physician.

Dosage

Sephience should be administered orally once daily.

The recommended dose of Sephience (mg/kg/day) for a single oral administration depends on age and body weight (see Table 1).

For patients ≥ 2 years of age, the recommended dose is 60 mg/kg, which is also the maximum dose. Lower doses may be used at the doctor's discretion (see also “Clinical efficacy”).

For patients < 2 years of age, the standard doses in Table 1 are intended. If the response to the standard dose is insufficient, the dose may be gradually increased to a maximum of 60 mg/kg.

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*

*Maximum daily dose for patients aged ≥2 years.

Response to treatment

The determination of responsiveness and treatment discontinuation in case of a non-response is at the discretion of the treating physician and is based on a therapeutic phenylalanine target value in the blood, which is individually defined for each patient.

In the Phase 3 clinical trial relevant for approval, a response was defined as a reduction of at least 15% in blood phenylalanine (Phe) levels after 14 days of treatment with sepiapterin.

No controlled data on efficacy and safety are available in patients who did not reach this threshold.

Delayed or missed doses

A missed dose should be taken as soon as possible on the same day, and the normal dosing schedule should be resumed the following day. Missed doses should not be taken the following day.

Special patient groups

Elderly

The safety and efficacy of Sephience have not been studied in patients aged 65 years and older. Caution should be exercised when prescribing to patients aged 65 years and older.

Renal or hepatic impairment

The safety and efficacy of Sephience have not been studied in patients with renal or hepatic impairment. Caution should be exercised when prescribing to such patients.

Method of administration

Sephience should be administered orally once daily at the same time each day with food.

As HPA due to PKU is a chronic condition, Sephience is intended for long-term use.

For patients weighing up to 16 kg

Sephience should be mixed with water or apple juice (9 ml per 250 mg sachet, 36 ml per 1000 mg sachet). The prepared mixture should be mixed well for 30 seconds or longer until it is uniform and free of lumps. The dose volume to be administered according to Tables 2-5 should be drawn up using an application syringe (PP/PE) or an enteral feeding tube (made of silicone or polyurethane) and the drawn-up dose should be administered immediately. To ensure that the dose is completely administered, the syringe or probe should be rinsed with additional water or juice and the contents swallowed immediately.

Tables 2 to 5 below contain the dose volumes for standard dosages for pediatric patients weighing up to 16 kg.

Table 2: Dosing table for patients aged 0 to less than 6 months

Dose and Age	**7.5 mg/kg/day**		
	0 to <6 Months		
Weight (kg)	**Total Dose (mg)**	**Number of Sachets (250 mg)**	**Administered Dose Volume (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	3.0
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: Dosing table for patients aged 6 to less than 12 months

Dose and Age	15 mg/kg/day		
	6 Months to <12 Months		
Weight (kg)	Total Dose (mg)	Number of Sachets (250 mg)	Administered Dose Volume (mL)
2	30	1	1.2
3	45	1	1.8
4	60	1	2.4
5	75	1	3.0
6	90	1	3.6
7	105	1	4.2
8	120	1	4.8
9	135	1	5.4
10	150	1	6.0
11	165	1	6.6
12	180	1	7.2
13	195	1	7.8
14	210*	1	8.4
15	225*	1	9.0
16	240*	1	9.6

*One full 250 mg sachet can be administered using a container instead of a syringe.

Table 4: Dosing table for patients aged 12 months to less than 2 years

Dose and Age	30 mg/kg/day		
	12 Months to <2 Years		
Weight (kg)	Total Dose (mg)	Number of Sachets (250 mg)	Administered Dose Volume (mL)
2	60	1	2.4
3	90	1	3.6
4	120	1	4.8
5	150	1	6.0
6	180	1	7.2
7	210	1*	8.4
8	240	1*	9.6
9	270	2*	10.8
10	300	2*	12.0
11	330	2	13.2

12	360	2	14.4
13	390	2	15.6
14	420	2**	16.8
15	450	2**	18.0
16	480	2**	19.2

*One full 250 mg sachet can be administered using a container instead of a syringe.
**Two full 250 mg sachets can be administered using a container instead of a syringe.

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

Dose and Age	**60 mg/kg/day**		
	≥2 Years		
Weight (kg)	**Total Dose (mg)**	**Number of Sachets Dissolved (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

*Four full 250 mg sachets or 1 full sachet of 1000 mg can be administered using a container (PP/PE container) instead of a syringe.

For patients weighing 16 kg or more

For patients weighing 16 kg or more, the daily dose should be rounded up or down to the nearest multiple of 250 mg or 1000 mg. For example, a calculated dose of 1251 to 1374 mg should be rounded down to 1250 mg, or a calculated dose of 1375 to 1499 mg should be rounded up to 1500 mg.

The entire contents of each Sephience sachet should be mixed with water or apple juice (10 ml for each 250 mg sachet, 20 ml for each 1000 mg sachet) or with soft food (2 tablespoons in total). The powder should be mixed well with water or apple juice for at least 30 seconds and with soft food for at least 60 seconds. The mixed dose should be administered immediately.

To ensure that the dose is completely administered, the container should be rinsed with additional water or juice and the contents swallowed immediately.

Administration via an enteral feeding tube

Sephience powder for oral use can be administered via an enteral feeding tube after mixing with water. Follow the instructions of the manufacturer of the feeding tube to administer the medicine. See also section “Other information”.

For instructions on how to prepare Sephience before use, see the section “Other information.”

Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section “Composition.”

Warnings and precautions

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

Monitor patients when co-administering Sephience and medications known to be inhibitors of dihydrofolate reductase.

Co-administering Sephience with inhibitors of dihydrofolate reductase (DHFR) (eg, 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 tetrahydrobiopterin (BH_4) by inhibiting the enzyme DHFR.
Patients with the rare hereditary fructose intolerance should not use this medicine.

Isomalt:
Patients with the rare hereditary fructose intolerance should not use this medicine.

Sodium:
This medicine contains less than 1 mmol sodium (23 mg) per 250 mg and 1000 mg sachet and is almost “sodium-free.”

Interactions

Drug interactions with Sephience
In vitro studies indicate that sepiapterin and BH_4 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 healthy subjects, administration of a single dose of sepiapterin at the maximum therapeutic dose of 60 mg/kg had no effect on the pharmacokinetics (PK) of a single dose of rosuvastatin, a breast cancer resistance protein (BCRP) substrate, administered concomitantly. Following co-administration with sepiapterin, geometric mean ratios (GMRs) for rosuvastatin exposure (maximum observed concentration [C_{max}] and area under the concentration-time curve from time zero to time of the last quantifiable measurement [$AUC_{0\text{-}last}$]) were 1.13 (1.00-1.28) and 1.02 (0.93-1.13), respectively, when compared with rosuvastatin alone.

Effects of other medicinal products on Sephience

Oral co-administration of BCRP inhibitors (ie, curcumin [2 g]) does not lead to a clinically relevant increase in exposures to sepiapterin and BH_4. Following co-administration of sepiapterin with curcumin, GMRs for BH_4 exposure (C_{max} and $AUC_{0\text{-}last}$) were 1.24 (1.15-1.33) and 1.20 (1.13-1.28), respectively, when compared with sepiapterin alone.

Concomitant administration of drugs known to inhibit folate synthesis via DHFR (eg, trimethoprim, methotrexate, pemetrexed, pralatrexate, and trimetrexate) may interfere with sepiapterin and BH_4 metabolism. Caution is recommended when using such medicinal products while taking Sephience.

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 sulphasalazine or sulphamethoxazole.

Pregnancy, lactation

Pregnancy

There is very limited experience to date with the use of Sephience in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproduction toxicity. Experimental animal studies did not show any evidence of direct or indirect adverse health effects in relation to reproductive toxicity (see section “Preclinical Data”). The use of Sephience should only be considered if strict dietary treatment does not adequately reduce Phe blood levels.

Caution should be exercised when prescribing to pregnant women.

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 “Preclinical data”).

Effects on ability to drive and use machines

No corresponding studies have been carried out.
According to the known safety profile, Sephience is expected to have no or a negligible effect on the ability to drive or operate machinery.

Undesirable effects

Summary of the safety profile
The safety profile for sepiapterin is based on clinical trials in the PKU population, which involved both paediatric and adult patients who received sepiapterin at doses ranging from 20 to 60 mg/kg/day.

Tabulated list of adverse reactions
The overall frequency of adverse reactions to sepiapterin, presented in Table 6, was calculated based on pooled data from the 2 pivotal studies in patients with PKU, PTC923-MD-003-PKU and PTC923-MD-004-PKU.
Adverse reactions are organized by MedDRA System Organ Class (SOC). Within each SOC, Preferred Terms (PTs) are arranged in decreasing frequency. Frequencies of occurrence are defined as “very common” (≥1/10); “common” (≥1/100 to <1/10); “uncommon” (≥1/1000 to <1/100); “rare” (≥1/10,000 to <1/1000); “very rare” (<1/10,000); and “not known” (cannot be estimated from available data).
No adverse reactions with “uncommon,” “rare,” “very rare,” or with “not known” frequency were identified for sepiapterin in clinical trials in patients with PKU.

Table 6: Adverse reactions for sepiapterin in the treatment of HPA in adult and paediatric patients with PKU (pooled analysis)

MedDRA System Organ Class	**Frequency**	**Frequency**
	Very Common	**Common**
Infections and infestations	Upper respiratory tract infection	-
Nervous system disorders	Headache	-
Gastrointestinal disorders	Diarrhoea Abdominal pain*	Faeces discoloured

Abbreviations: HPA, hyperphenylalaninemia; PKU, phenylketonuria
*Grouping of more than one MedDRA preferred term.

Most adverse reactions for sepiapterin included in Table 6 occurred in the ≥18 years and ≥12 to <18 years age groups and all were of mild intensity. Overall, in PKU clinical trials, sepiapterin was well tolerated in paediatric patients, and in general, the incidence and nature of treatment-related

adverse events in all age groups of children were consistent with those observed in adults. No significant laboratory findings, inclusive of indicators of renal or hepatic dysfunction, were observed in adult and paediatric patients treated with sepiapterin in PKU clinical trials. Long-term safety data are not available.
The reporting of suspected adverse reactions after authorisation is of great importance. It enables continuous monitoring of the risk-benefit ratio of the medicinal product. Healthcare professionals are requested to report any suspicion of a new or serious adverse reaction via the online portal EIViS (Electronic Vigilance System). Information on this can be found at www.swissmedic.ch.

Overdose

Higher doses than the recommended maximum daily dose have been evaluated in clinical studies (80 mg/kg/day). The acute effects of overdose have not been evaluated. The mode of action does not indicate Sephience has abuse potential or would evoke a withdrawal or rebound effect.
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.

Properties/Effects

ATC-Code

A16AX28

Mechanism of action

Sepiapterin is a natural precursor of the enzymatic co-factor BH_4, a critical co-factor for phenylalanine hydroxylase (PAH). Sepiapterin acts as a dual pharmacological chaperone (sepiapterin and BH_4, each with its own binding affinity to variant PAH), including PAH variants commonly found in PKU and known to be insensitive to BH_4, including 10 of the 15 most common PAH variants known to be insensitive to BH_4, to improve the activity of the defective PAH enzyme, achieving a high concentration of BH_4 intracellularly. By enhancing the conformational stability of misfolded PAH enzyme and increasing the intracellular concentrations of BH_4, sepiapterin is able to effectively reduce blood Phe levels.

Pharmakodynamics

Cardiac electrophysiology

A clinical study was conducted to assess QT interval prolongation risks in adult healthy subjects. The results indicated that there was a negligible central trend with increase of placebo adjusted QTcF change from baseline with sepiapterin or BH_4 concentrations, and sepiapterin dose up to 120 mg/kg administered with a high-fat diet was well tolerated and not associated with QT prolongation. A shortened QT interval was observed with increased BH_4 concentration. However, this was deemed

not clinically relevant, as the maximum reduction in QTcF was -2.13 ms (90% CI: -3.47, -0.79 ms) at the geometric mean of baseline corrected BH_4 C_{max} of 732.38 ng/mL, which was less than the QTcF shorten of -5.78 ms postprandial.

Clinical efficacy

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, randomized, placebo-controlled study of 157 patients with PKU of all ages.

Part 1 of the study tested 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 randomized 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. 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.

At baseline, mean blood Phe was similar between the sepiapterin and placebo groups (Table 7; Figure 1).

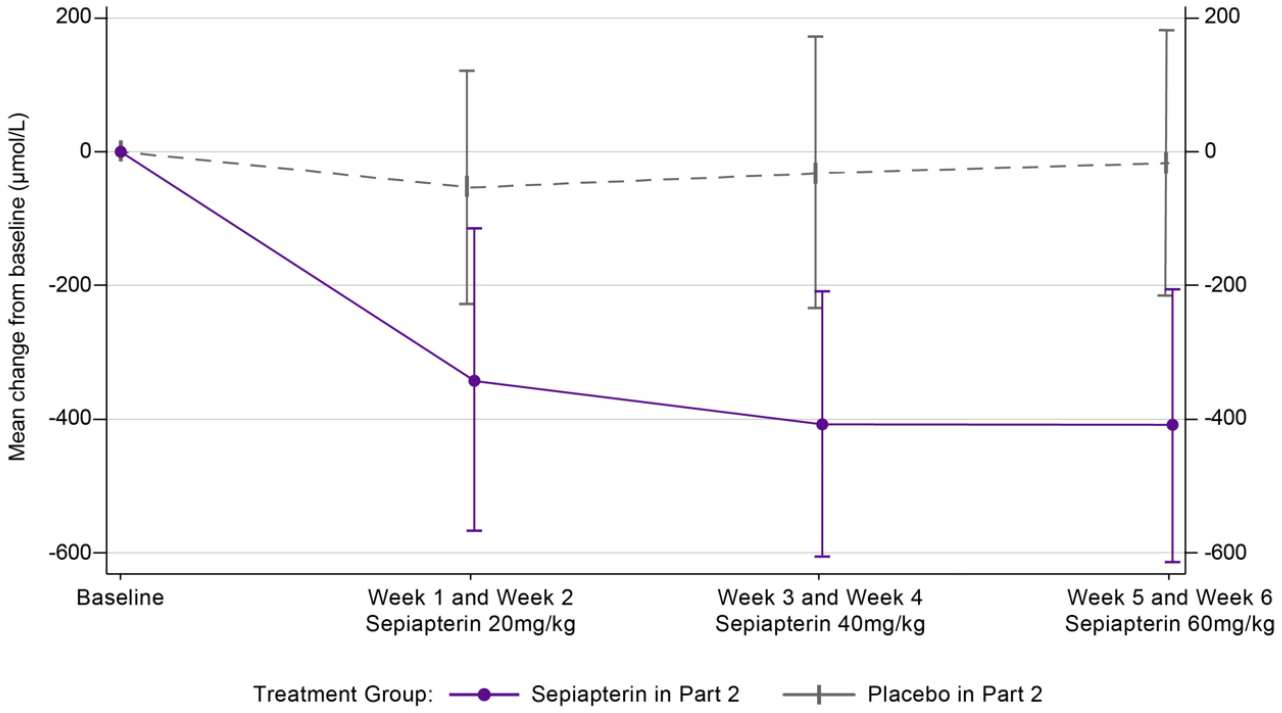
Table 7: Mean Change in Blood Phe Levels from Baseline to Week 5 and Week 6 in Part 2 (Primary Analysis Set with Phe Reduction from Baseline ≥30% during Part 1)

	Sepiapterin (N=49)	Placebo (N=49)	Difference Sepiapterin vs Placebo	p Value
Baseline*				
n	49	49	-	
Mean (SD)	646.11 (253.007)	654.04 (261.542)		
Weeks 5 and 6**				
n	49	49	-	
Mean (SD)	236.04 (174.942)	637.85 (259.886)		
Mean (SD) change from baseline (µmol/L)	-410.07 (204.442)	-16.19 (198.642)		
Mean (SD) 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)	

Abbreviations: 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 postbaseline 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).

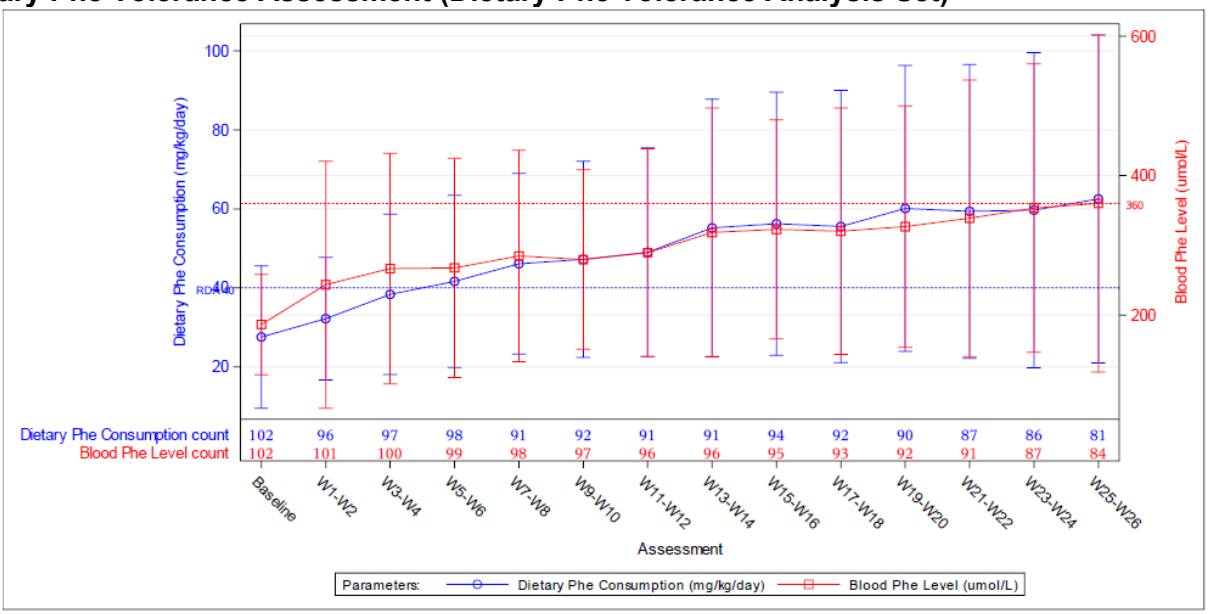
Figure 1: Mean (SD) Change in Blood Phe Levels from Baseline to Week 5 and Week 6 in Part 2 (Primary Analysis Set with Phe Reduction from Baseline ≥30% during Part 1)



Abbreviations: Phe, phenylalanine; SD, standard deviation.

Study 3 (PTC923-MD-004-PKU) is an ongoing, Phase 3, multicentre, open-label study to assess the safety and dietary Phe tolerance during long-term treatment with sepiapterin in patients with PKU. Interim data from 169 patients received treatment with Sephience 7.5 mg/kg in participants 0 to <6 months of age, 15 mg/kg in participants 6 to <12 months of age, 30 mg/kg in participants 12 months to <2 years of age, or 60 mg/kg in participants ≥2 years of age per day. Interim data indicate that daily sepiapterin administration is associated with an approximately 2.3-fold increase in mean daily Phe consumption (27.1 mg/kg/day at baseline versus 62.5 mg/kg/day at Week 26).

Figure 2: Mean (SD) Dietary Phe Consumption and Blood Phe Concentration Over Time During Dietary Phe Tolerance Assessment (Dietary Phe Tolerance Analysis Set)



Abbreviations: Phe, phenylalanine; RDA, recommended daily amount; SD, standard deviation; W, week

Note: Baseline is defined as the average of daily dietary Phe consumption (mg/kg/day) at Month 1. This figure summarises the data collected as part of the dietary Phe tolerance assessment. Lower dotted line represents the RDA for an adult with PKU, which is 0.8 g protein/kg (equivalent to approximately 40 mg/kg/day of Phe). Upper dotted line shows recommended blood Phe concentration.

These data suggest that sepiapterin treatment may allow liberalization of the highly restrictive diet that patients with PKU must adhere to. At the time of the data cutoff date, no QOL analyses were available.

Pharmacokinetics

Absorption

Following oral administration, sepiapterin is quickly absorbed, and the peak plasma concentrations occur in approximately 1 to 3 hours. The C_{max} was approximately 2.80 ng/mL following a 60 mg/kg dose 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 BH_4, and the time to maximum observed concentration (T_{max}) was approximately 4 hours. Both BH_4 C_{max} and 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 BH_4 following repeated doses of sepiapterin up to 60 mg/kg.

Effect of food

When 60 mg/kg sepiapterin was administered with a low-fat, low-calorie meal , BH_4 exposures were 1.72-fold higher for C_{max} and 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, BH_4 exposures

were 2.21-fold higher for C_{max} and 2.84-fold higher for AUC_{0-24h} compared to administration under fasted conditions.

Distribution

In vitro studies show that sepiapterin is bound (mean 15.4%) to plasma protein in the presence of 0.1% dithiothreitol. BH_4 were 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 BH_4 concentration was observed in the cerebrospinal fluid following repeated sepiapterin oral administration.

Metabolismus

Sepiapterin is metabolised by SR/carbonyl reductase and DHFR in a 2-step unidirectional process to form BH_4. The metabolism of BH_4 is presumed to follow the same pathway as endogenous BH_4 oxidized while acting as coenzymes for aromatic amino acid hydroxylases, such as phenylalanine hydroxylase, tyrosine hydroxylase, tryptophan hydroxylase, alkylglycerol monooxygenase, and nitric oxide synthase, and some metabolites, like 4α-hydroxy-tetrahydrobiopterin and quinonoid dihydrobiopterin, could be recycled to regenerate BH_4 by pterin-4α-carbinolamine dehydratase and dihydropteridine reductase.
Extensive metabolism of sepiapterin was observed in humans 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

Plasma sepiapterin declined rapidly following C_{max} to below the limit of quantitation, generally by 12 hours postdose. Plasma BH_4 declined mono exponentially following C_{max}. The terminal half-life was approximately 5 hours.
Following oral administration in healthy participants, sepiapterin was extensively metabolised with the metabolites excreted primarily in faeces.
Following a single oral dose of ^{14}C-sepiapterin to adult healthy subjects, a mean of 6.7% dosed radioactivity was recovered in urine and 26.2% in faeces with the combined total recovery of 32.9% by 240 hours. The majority of radioactivity was recovered within the first 48 hours postdose (28.2%). The total renal clearance of radioactivity derived from ^{14}C-sepiapterin was 1.536 L/h (25.6 mL/min).
An in vitro study in human intestinal microbiota indicated that volatile metabolite(s) were formed. The low total mass recovery (mean of 32.9%) in humans following a single dose ^{14}C-sepiaterin could be attributed to the volatile metabolite formation in human intestine.

Specific Populations

Patients with renal impairment

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

Patients with hepatic impairment

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

Pediatric patients

The pharmacokinetics of sepiapterin have been studied in patients of all age groups, although data in patients <1 year of age are limited. Apart from weight-based allometric effects on clearance and distribution volume, no other age-related effects were demonstrated in the population PK study. The simulated BH_4 levels in pediatric patients compared to patients over 16 years of age (median and 90% confidence interval AUC at steady state) at the standard dosage are shown in Table 8:

Table 8: Summary of PK Exposures (< 2 years) – By Age Group

Age Group	**Dose (mg/kg)**	**AUC_{ss} (ng*h/mL) Median [5% - 95% KI]**
above 16 years	60	2496 [1425 – 4859]
12 to 15 years	60	2437 [1425 – 4285]
6 to 11 years	60	2232 [1386 – 4239]
2 to 5 years	60	1912 [1032 – 3390]
12 to 24 months	30	1208 [640 – 2174]
6 to 12 months	15	922 [506 – 1650]
0 to 6 months	7.5	697 [429 – 1432]

Special patient groups

Asian participants showed higher exposures BH_4. In the population PK analysis, Asian patients showed an average 33% higher AUC_{ss} and a 36% higher C_{max}. No significant differences in BH_4 exposure were observed in the Hispanic population. No differences were observed between women and men.

Preclinical data

Repeated dose toxicity

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.
No findings occurred at BH_4 exposures that were 2-fold the human BH_4 exposures in the maximum recommended human dose (MRHD).

Genotoxicity and carcinogenicity

Sepiapterin was not mutagenic in bacterial mutagenicity tests but showed clastogenic potential in an in vitro chromosome aberration test without metabolic activation. Sepiapterin was not genotoxic in an in vivo micronucleus test and a Comet assay in rats.
In the 26-week oral carcinogenicity study in transgenic mice, no carcinogenic effect was observed at a BH_4 exposure that was 11-15 times higher than the human BH_4 exposure at 60 mg/kg/day.

Reproduction toxicity

No sepiapterin-related effects were observed on fertility, early embryonic development, or pre- and postnatal development at BH_4 exposure levels 7 times the human BH_4 exposure levels at the MRHD.
No sepiapterin-related adverse effects on embryo-foetal development were observed in pregnant rats and rabbits corresponding to BH_4 exposure levels 9 and 6 times, respectively, the human BH_4 exposure levels at the MRHD.
In the juvenile toxicology study, no sepiapterin-related effects were observed in rats at BH_4 exposure levels 4 times the human BH_4 exposure levels at the MRHD.

Other information

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Shelf life after opening

The liquid mixture is not preserved. For microbiological reasons, each prepared dose is best administered immediately after preparation. The prepared dose should be discarded if not used within 24 hours of preparation when kept refrigerated (2°C to 8°C) or within 6 hours at below 25°C. The mixture should be stored away from light from the time of preparation until administration.

Special storage conditions

Keep out of reach of children and do not store above 25°C.
Keep in the original package (sachet) to protect from light and moisture.

Instructions for handling

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed in accordance with local requirements.

For patients weighing 16 kg or less

Sephience should be mixed with water or apple juice (9 mL for each 250 mg sachet), and a portion of this mixture corresponding to a required dose should be administered orally via an oral dosing syringe (PP or PE). If not administered immediately, the liquid mixtures can be administered within 6 hours (if

stored at room temperature) or 24 hours (if stored in the refrigerator) (to be taken at the same time each day) when stored at room temperature or in the refrigerator, respectively. The preparation should be mixed well for 30 seconds or more until uniform and free of lumps before drawing into the dosing syringe. Once drawn up, the dose should be administered immediately. To ensure complete delivery of the dose, rinse the syringe with additional water or juice and swallow the contents immediately.

For patients weighing 16 kg or more

Sephience sachets should only be opened at the time of dose preparation. The full content of each sachet should be mixed in water or apple juice (10 mL for each 250 mg sachet; 20 mL for each 1000 mg sachet) or with soft food (2 tablespoons). The powder should be mixed well for at least 30 seconds with water or apple juice and for at least 60 seconds with soft foods. Once mixed, the dose should be administered immediately. If not administered immediately, the liquid mixture can be administered within 6 (if stored at room temperature) or 24 hours (if stored in the refrigerator) (to be taken at the same time each day), when stored at room temperature or in the refrigerator, respectively. If not administered immediately, the liquid (suspension) and soft food mixtures should be mixed once again for at least 30 seconds and 60 seconds, respectively, before administration. To ensure complete delivery of the dose, rinse the container with additional water or juice and swallow the contents immediately.

Administration via an 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 “Dosage/Administration”).
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.

Authorisation number

69810

Packs

Sephience 250 mg: Each folding box contains 30 single-dose sachets [B].
Sephience 1000 mg: Each folding box contains 30 single-dose sachets [B].

Marketing authorisation holder

PTC Therapeutics Switzerland GmbH, Steinhausen

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