29 April 2025
EMA/OD/0000157789
EMADOC-1700519818-2099472
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Sephience ((S)-2-amino-6-(2-hydroxypropanoyl)-7,8-dihydropteridin-4(3H)-one)
Treatment of hyperphenylalaninaemia
EU/3/21/2435

Sponsor: PTC Therapeutics International Limited

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Product and administrative information

Product	
Designated active substance	(S)-2-amino-6-(2-hydroxypropanoyl)-7,8-dihydropteridin-4(3H)-one
Other names	Sephience, Sepiapterin
International Non-Proprietary Name	Sepiapterin
Tradename	Sephience
Orphan condition	Treatment of hyperphenylalaninaemia
Sponsor's details:	PTC Therapeutics International Limited Unit 1 52-55 Sir John Rogerson's Quay Dublin 2 Co. Dublin D02 NA07 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	PTC Therapeutics International Limited
COMP opinion	15 April 2021
EC decision	20 May 2021
EC registration number	EU/3/21/2435
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Fátima Ventura / Alexandre Moreau
Applicant	PTC Therapeutics International Limited
Application submission	28 March 2024
Procedure start	23 May 2024
Procedure number	EMA/H/C/006331/0000
Invented name	Sephience
Approved therapeutic indication	Sephience is indicated for the treatment of hyperphenylalaninaemia (HPA) in adult and paediatric patients with phenylketonuria (PKU). Further information on Sephience can be found in the European public assessment report (EPAR) on the Agency's website : https://www.ema.europa.eu/en/medicines/human/EPAR/Sephience
CHMP opinion	25 April 2025
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Joao Rocha / Cécile Dop
Sponsor's report submission	31 May 2024
COMP discussion	14-15 April 2025
COMP opinion (adoption via written procedure)	29 April 2025

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2021 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing (S)-2-amino-6-(2-hydroxypropanoyl)-7,8-dihydropteridin-4(3H)-one was considered justified based on preliminary clinical data showing reduction of elevated blood phenylalanine levels;
- the condition is chronically debilitating (if untreated) due to high blood phenylalanine levels which cause cognitive impairment;
- the condition was estimated to be affecting approximately 1.9 in 10,000 persons in the European Union, at the time the application was made;

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (S)-2-amino-6-(2-hydroxypropanoyl)-7,8-dihydropteridin-4(3H)-one will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate reduction of elevated blood phenylalanine levels that cannot be achieved with the currently authorised products. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are cumulatively fulfilled. The COMP therefore recommends the designation of this medicinal product, containing (S)-2-amino-6-(2-hydroxypropanoyl)-7,8-dihydropteridin-4(3H)-one as an orphan medicinal product for the orphan condition: treatment of hyperphenylalaninaemia.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

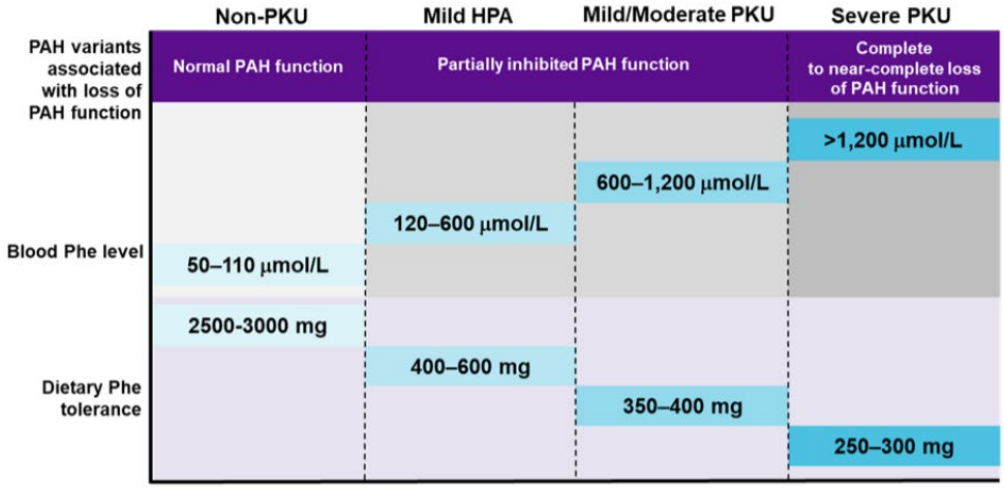
Hyperphenylalaninaemia (HPA) is a rare, serious, autosomal-recessive inborn error of phenylalanine (Phe) metabolism.

Primary HPAs are a group of inherited diseases due to defective phenylalanine hydroxylase (PAH) activity resulting in the accumulation of Phe in blood and other tissues (Smith 2000, de Baulny 2007). In most cases (98% of subjects), HPA results from mutations in the PAH gene. The associated phenotypes range in severity from classic phenylketonuria (PKU) to mild HPA. The remaining cases of

HPA arise due to a block in the metabolism of the cofactor tetrahydrobiopterin (BH4) and pathogenic variants in the DNAJC12 gene. Less common secondary causes of HPA are associated with neonatal prematurity, a high dietary protein intake, liver or renal diseases, and drugs (methotrexate, trimethoprim) (Smith 2000).

PKU, known as "classical PKU" (cPKU), have highly elevated blood Phe concentrations (≥1200 µmol/L) that, if left untreated, is a significant risk factor for severe irreversible neurological dysfunction and intellectual disability with impaired cognitive function (Scriver and Kaufman 2001, Waisbren 2007). The severity of PKU is defined by blood Phe concentration, dietary Phe tolerance, and PAH function (Figure below with classification of PKU Disease Severity).

Figure 1. Classification of PKU Disease Severity



Abbreviations: HPA, hyperphenylalaninaemia; PAH, phenylalanine hydroxylase; Phe, phenylalanine; PKU, phenylketonuria; Note: Daily Phe tolerance values presented are for adults.
Source: Adapted from (Blau 2010, Hillert 2020)

PKU is diagnosed at birth as part of routine newborn screening. Newborns with PKU can appear normal at birth, with symptoms (e.g., fair skin, eczema, seizures, tremors, and hyperactivity) appearing after several months.

In patients with PKU on an unrestricted diet or not adequately controlled, sustained elevation of blood Phe concentration above normal levels occur which is neurotoxic. There is a direct association between elevated blood Phe concentration and a range of symptoms including the development of neurocognitive deficits, severe and irreversible intellectual disability, memory impairment, and psychiatric and behavioural problems even in adolescence and adults with the disease (Waisbren 2007, Ashe 2019, Kaufman 1989, Channon 2007, Moyle 2007, VanZutphen 2007, Feldmann 2019).

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.

The proposed therapeutic indication "Sephience is indicated for the treatment of hyperphenylalaninaemia (HPA) in adult and paediatric patients with phenylketonuria (PKU)" falls within the scope of the designated orphan condition "Treatment of hyperphenylalaninaemia".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

The sponsor conducted an updated review of literature to identify any relevant changes in seriousness of the condition. The sponsor has not identified any significant changes in the seriousness of HPA since the orphan designation was granted, and no new therapies have been approved.

PKU is a chronic, devastating disease that dramatically impacts patients' health and quality of life (QOL). Hyperphenylalaninaemia results in the development of neurological disorders, and a significant negative impact on indices of QOL. Uncontrolled HPA in patients with PKU, especially in children and adolescents, causes severe and irreversible neurological dysfunction, including impaired cognitive function and processing, behavioural problems, attention hyperactivity disorder, motor dysfunction, and additional psychiatric and emotional symptoms. A direct association has been documented between blood Phe concentration in patients with PKU on an unrestricted diet and the development of severe intellectual disability (Waisbren et al., 2007). Untreated HPA leads to progressive developmental delays and severe irreversible intellectual disability (Waisbren et al., 2007), accompanied by a host of additional symptoms such as growth failure, hypopigmentation, eczematous rash, motor deficits, ataxia, and seizures (Al Hafid et al., 2015; Burton et al., 2018; van Vliet et al., 2018). Aberrant behaviour, deficits in executive functioning, psychiatric symptoms, and memory impairment may also develop in affected individuals (Blau et al., 2010).

No significant changes have occurred in the chronically debilitating and life-threatening nature of the condition since the orphan designation in 2021. The COMP has previously accepted that the clinical course of hyperphenylalaninaemia can be chronically debilitating due to intellectual impairment, deterioration of cognitive performance and motor skills, and heterogeneous psychiatric deficits that have a significant impact on daily living. The severe nature of hyperphenylalaninaemia earlier acknowledged by the COMP remains acceptable for this procedure.

Number of people affected or at risk

At the time of the orphan designation in 2021, the COMP concluded that the condition was estimated to be affecting approximately 1.9 in 10,000 persons in the European Union (EU). The sponsor re-assessed the prevalence of HPA through rigorous literature searches carried out to retrieve new articles that would have been published since the compilation of the original orphan drug designation application *i.e.* 2021 to 2024 and that could provide data enabling an update of the estimate of the current prevalence of HPA in the European Community (EC).

- From the literature search, two recent articles have been retrieved as relevant for the PKU prevalence in Europe: (Chen et al., 2022; Elhawary et al., 2022) reporting PKU prevalence based on epidemiological data from an article published in 2020 (Hillert et al., 2020), already mentioned in the initial ODD application.
- The prevalence of HPA varies worldwide. In Europe, the prevalence ranges from 1:2,700 live births in Italy to <1:100,000 live births in Finland (Chen et al., 2022; Hillert et al., 2020).
- The reported PKU prevalence and calculated HPA prevalence per 10,000 for each country in Europe (including Iceland, Liechtenstein and Norway) are displayed in the Table 1.

Table 1. Reported PKU prevalence and calculated HPA prevalence per 10,000 for each country in Europe

Reference	Location	Reported PKU prevalence	PKU Prevalence per 10,000	Calculated HPA prevalence per 10,000*
(Elhawary et al., 2022)	Austria	1:5764	1.73	1.78
(Loeber, 2007)	Belgium	Flanders 1:32733 Wallonia 1:15499	Flanders: 0.30 Wallonia: 0.64	Flanders: 0.31 Wallonia: 0.65
(Elhawary et al., 2022)	Bulgaria	1:26695	0.37	0.39
(Elhawary et al., 2022)	Croatia	1:8333	1.20	1.22
(Elhawary et al., 2022)	Cyprus	1:13000	0.77	0.79
(Elhawary et al., 2022)	Czech Republic	1:5753	1.74	1.77
(Elhawary et al., 2022)	Denmark	1:13434	0.74	0.76
(Hillert et al., 2020)	Estonia	1:7143	1.40	1.43
(Hillert et al., 2020)	Finland	1:112000	0.09	0.09
(Elhawary et al., 2022)	France	1:9091	1.10	1.12
(Elhawary et al., 2022)	Germany	1:5360	1.86	1.90
(Elhawary et al., 2022)	Greece	1:10420	0.96	0.98
(Hillert et al., 2020)	Hungary	1:9000	1.11	1.13
(Hillert et al., 2020)	Iceland	1:8400	1.19	1.21
(Elhawary et al., 2022)	Ireland	1:4545	2.20	2.24
(Elhawary et al., 2022)	Italy	1:4000	2.5	2.55
(Hillert et al., 2020)	Latvia	1:8170	1.22	1.25
NA	Liechtenstein	Not available		
(Hillert et al., 2020)	Lithuania	1:9300	1.08	1.10
NA	Luxembourg	Not available		
(Elhawary et al., 2022)	Netherlands	1:11546	0.86	0.88
(Elhawary et al., 2022)	Norway	1:11457	0.87	0.90
(Hillert et al., 2020)	Poland	1:8309	1.20	1.23
(Elhawary et al., 2022)	Portugal	1:12500	0.8	0.82
(Hillert et al., 2020)	Romania	1:10000	1	1.02
(Elhawary et al., 2022)	Spain	1:10115	0.99	1.00
(Elhawary et al., 2022)	Sweden	1:12681	0.79	0.80

*HPA calculated assuming mutations in *PAH* gene accounts for 98% of PKU cases (Ho et al., 2014)

There are major disparities between European countries, and the estimated HPA prevalence ranges between 0.09 per 10,000 in Finland to 2.55 per 10,000 in Italy. In order to keep a conservative approach, the sponsor considers that the HPA prevalence in EC is estimated at 2.55 per 10,000 inhabitants.

The COMP considers that the proposed prevalence is conservative since it reflects the highest prevalence reported in the EU and considers that the prevalence of less than 2 which was recently adopted should be retained.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Dietary treatment is the basis of PKU management. It consists of 3 parts: natural protein restriction, Phe-free-L-amino acid supplements, and low protein food. The majority of patients fail to achieve adequate low phenylalanine levels based on the diet alone.

There are currently two approved pharmacological treatments for HPA in the EU: Palynziq (pegvaliase-pqpz) and Kuvan (sapropterin dihydrochloride).

Pegvaliase-pqpz is a polyethylene glycol(PEG)-ylated recombinant phenylalanine ammonia lyase (rAvPAL), derived from the Cyanobacterium Anabaena variabilis expressed in *Escherichia coli* (*E. coli*). Palynziq is indicated for the treatment of patients with PKU aged 16 years and older who have inadequate blood phenylalanine control (blood phenylalanine levels greater than 600 micromol/l) despite prior management with available treatment options.

Since Palynziq is authorised only for patients the treatment of patients with PKU aged 16 years and older its will not be considered as satisfactory method because Sephience covers paediatric patients as well and therefore it has a broader indication.

Kuvan (sapropterin dihydrochloride) is indicated for the treatment of hyperphenylalaninaemia (HPA) in adults and paediatric patients of all ages with PKU who have been shown to be responsive to such treatment. Kuvan is also indicated for the treatment of HPA in adults and paediatric patients of all ages with tetrahydrobiopterin (BH4) deficiency who have been shown to be responsive to such treatment.

The below is also under section 4.2 of the SmPC of Kuvan:

It is of primary importance to initiate treatment as early as possible to avoid the appearance of non-reversible clinical manifestations of neurological disorders in paediatric patients and cognitive deficits and psychiatric disorders in adults due to sustained elevations of blood phenylalanine.

Response to this medicinal product is determined by a decrease in blood phenylalanine. Blood phenylalanine levels should be checked before administering Kuvan and after 1 week of use at the recommended starting dose. If an unsatisfactory reduction in blood phenylalanine levels is observed, then the dose can be increased weekly to a maximum of 20 mg/kg/day, with continued weekly monitoring of blood phenylalanine levels over a one-month period. The dietary phenylalanine intake should be maintained at a constant level during this period.

A satisfactory response is defined as a ≥30 percent reduction in blood phenylalanine levels or attainment of the therapeutic blood phenylalanine goals defined for an individual patient by the treating physician. Patients who fail to achieve this level of response within the described one-month test period should be considered non-responsive, these patients should not be treated with Kuvan and the administration of Kuvan should be discontinued.

Kuvan is only indicated for the treatment of HPA in adults and paediatric patients of all ages with PKU who have been shown to be "responsive to such treatment". As sepiapterin will cover also the patient population who is not responded to Kuvan, it is considered to have a broader indication. Therefore, Kuvan is not also considered as satisfactory method.

Of note, while the restriction of the indication of Kuvan excludes it formally from being defined as satisfactory method (in spite of targeting the same essential co-factor) the clinical relevance of the difference in the wording of the therapeutic indication is supported by clinical data. Sepiapterin has shown efficacy in patients not responding to sapropterin. Additionally, in patients responding to sapropterin, sepiapterin significantly improved clinical response.

Significant benefit

Not applicable.

4. COMP position adopted on 29 April 2025

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of hyperphenylalaninaemia (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be less than 2 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to intellectual impairment, deterioration of cognitive performance and motor skills, and heterogeneous psychiatric deficits that have a significant impact on daily living;
- at present, no satisfactory method has been authorised in the European Union for the treatment of the entirety of patients covered by the therapeutic indication of Sephience.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Sephience, (S)-2-amino-6-(2-hydroxypropanoyl)-7,8-dihydropteridin-4(3H)-one, sepiapterin for treatment of hyperphenylalaninaemia (EU/3/21/2435) is not removed from the Community Register of Orphan Medicinal Products.