Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V: Sepiapterin (hyperphenylalaninaemia in phenylketonuria)

of 22 January 2026

At their session on 22 January 2026, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient Sepiapterin as follows:

Sepiapterin

Resolution of: 22 January 2026
Entry into force on: 22 January 2026
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 19 June 2025):

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

Therapeutic indication of the resolution (resolution of 22 January 2026):

See therapeutic indication according to marketing authorisation.

1. Extent of the additional benefit and significance of the evidence

Sepiapterin (Sephience) is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The G-BA determine the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5 Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5 Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

<u>Adults and paediatric subjects with phenylketonuria-associated hyperphenylalaninaemia (HPA)</u>

Extent of the additional benefit and significance of the evidence of sepiapterin:

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Study results according to endpoints:[1]

Adults and paediatric subjects with phenylketonuria-associated hyperphenylalaninaemia

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	There are no assessable data.
Morbidity	n.a.	There are no assessable data.
Health-related quality of life	∅	No data available.
Side effects	n.a.	There are no assessable data.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: No data available. n.a.: not assessable		

APHENITY study (PTC923-MD-003-PKU): controlled, randomised phase III study; sepiapterin vs placebo, study phase part 2, study participants with response to sepiapterin

Mortality

Endpoint	Sepiapterin		Placebo		Sepiapterin vs placebo
	N	**Patients with event** n (%)	N	**Patients with event** n (%)	**RR** [95% CI]; p value
Overall mortality					
	56	0 (0)	54	0 (0)	--

[1] Data from the dossier assessment of the G-BA (published on 15. October 2025), and from the amendment to the dossier assessment from 19 December 2025, unless otherwise indicated.

Morbidity

Endpoint	Sepiapterin			Placebo			Sepiapterin vs placebo
	N	Values at baseline[a] MV (SD)	Change at week 5/6[b] to baseline LS mean [95% CI]	N	Values at baseline[a] MV (SD)	Change at week 5/6[b] to baseline LS mean [95% CI]	LS mean difference [95% CI][c,d]; p value
Phe concentration in blood (primary endpoint; presented additionally)							
	56	645.6 (246.1)	-289.6 [-352.0; -227.2]	54	667.8 (264.6)	65.3 [0.07; 130.5]	-354.9 [-427.1; -282.7] < 0.0001

Health-related quality of life

No data available.

Side effects

Endpoint MedDRA system organ classes/ preferred terms/ AEs of special interest	Sepiapterin		Placebo		Sepiapterin vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI][e]; p value[f]
Total adverse events (presented additionally)	56	33 (58.9)	54	18 (33.3)	-
Serious adverse events (SAE)	56	0 (0)	54	0 (0)	-
Severe adverse events (CTCAE grade 3 or 4)	56	0 (0)	54	0 (0)	-
Therapy discontinuation due to adverse events	56	0 (0)	54	0 (0)	-
Severe adverse events according to MedDRA (with an incidence ≥ 5% in one study arm and statistically significant difference between the treatment arms; SOC and PT)					
No severe AEs ≥ 5%					
SAEs according to MedDRA (with an incidence ≥ 5% in one study arm and statistically significant difference between the treatment arms; SOC and PT)					
No SAE ≥ 5%					
a. MV of day -1 and 1 of the 2nd part of the study b. MV from weeks 5 and 6					

c. The analysis is based on an MMRM with the change from baseline as the dependent variable. The model contains baseline Phe values, treatment, visit, the interaction treatment*visit and the stratification factors Phe stratum at baseline (< 600 vs ≥ 600 µmol/l) and Phe reduction in part 1 (≥ 15% to < 30% vs ≥ 30 %) as fixed effects and patient as a random effect.
d. There were no significant differences in the estimated daily intake of phenylalanine over the course of the study.
e. RR values were calculated post hoc using generalised linear models. Where possible, all models were stratified by Phe values at baseline in study phase part 1 (< 600 vs ≥ 600 µmol/l) and Phe reduction in study phase part 1 (≥ 15% to < 30% vs ≥ 30%).
f. Cochran-Mantel-Haenszel test

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; CI = confidence interval; LS= least squares; MV= mean value; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; RR = relative risk; Phe= phenylalanine; SD= standard deviation; (S)AE= (serious) adverse event; vs = versus; - = not calculable

AMPLIPHY study (PTC923-PKU-301): actively controlled, randomised, open-label cross-over study; sepiapterin vs sapropterin, study phase 2, study participants with response to sepiapterin

Mortality

Endpoint	**Sepiapterin**		**Sapropterin**		**Sepiapterin vs sapropterin**
	N	**Patients with event** n (%)	N	**Patients with event** n (%)	**RR** [95% CI]; p value
Overall mortality					
	62	0 (0)	60	0 (0)	--

Morbidity

Endpoint	Sepiapterin			Sapropterin			Sepiapterin vs sapropterin
	N	**Values at baseline**[a] MV (SD)	**Change at week 3/4**[b] **to baseline** LS mean [95% CI]	**N**	**Values at baseline**[a] MV (SD)	**Change at week 3/4**[b] **to baseline** LS mean [95% CI]	**LS mean difference** [95% CI][c,d]; p value
Phe concentration in blood (primary endpoint; presented additionally)							
	62	718.8 (309.1)	-355.5 [n.d.]	60	782.7 (363.6)	-174.4 [n.d.]	-181.1 (-228.5; -133.7) < 0.0001

Health-related quality of life

No data available.

Side effects

Endpoint MedDRA system organ classes/ preferred terms/ AEs of special interest	Sepiapterin		Sapropterin		Sepiapterin vs sapropterin
	N	**Patients with event** n (%)	**N**	**Patients with event** n (%)	**RR** [95% CI]; p value
Total adverse events (presented additionally)	62	41 (66.1)	60	37 (61.7)	-
Serious adverse events (SAE)	62	0	60	0	-
Severe adverse events (CTCAE grade 3 or 4)	62	2 (3.2)	60	1 (1.7)	n.d.
Therapy discontinuation due to adverse events	62	0	60	0	-
Severe adverse events according to MedDRA (with an incidence ≥ 5% in one study arm and statistically significant difference between the treatment arms; SOC and PT)					
No severe AEs ≥ 5%					
SAEs according to MedDRA (with an incidence ≥ 5% in one study arm and statistically significant difference between the treatment arms; SOC and PT)					
No SAE ≥ 5%					

a. MV of day -1 and 1 of the 2nd part of the study
b. MV from weeks 3 and 4
c. The analysis is based on an MMRM with the change from baseline as the dependent variable. The model includes treatment, sequence, period, visit (weeks 1 and 2, weeks 3 and 4), the interaction baseline treatment*visit and the stratification factor Phe reduction in part 1 (≥ 20% to < 30% vs ≥ 30%) as fixed

effects and the baseline Phe value (for each period) as a covariate. Patient nested in sequence is additionally integrated as a random effect.

d. There were no significant differences in the estimated daily intake of phenylalanine over the course of the study.

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; CI = confidence interval; LS= least squares; MV= mean value; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; RR = relative risk; Phe= phenylalanine; SD= standard deviation; (S)AE= (serious) adverse event; vs = versus; - = not calculable

2. Number of patients or demarcation of patient groups eligible for treatment

Adults and paediatric subjects with phenylketonuria-associated hyperphenylalaninaemia

Approx. 4,700 to 6,800 patients

3. Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Sephience (active ingredient: sepiapterin) at the following publicly accessible link (last access: 13 October 2025):

https://www.ema.europa.eu/en/documents/product-information/sephience-epar-product-information_en.pdf

Treatment with sepiapterin should only be initiated and monitored by specialists who are experienced in the treatment of patients with phenylketonuria.

4. Treatment costs

Annual treatment costs:

Adults and paediatric subjects with phenylketonuria-associated hyperphenylalaninaemia (HPA)

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Sepiapterin	€ 37,590.13 - € 706,053.08

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 15 November 2025)

Costs for additionally required SHI services: not applicable

5. Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

Adults and paediatric subjects with phenylketonuria-associated hyperphenylalaninaemia (HPA)

- No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

6. Percentage of study participants at study sites within the scope of SGB V in accordance with Section 35a, paragraph 3, sentence 5 SGB V

The medicinal product Sephience is a medicinal product placed on the market from 1 January 2025.

The percentage of study participants in the clinical studies of the medicinal product conducted or commissioned by the pharmaceutical company in the therapeutic indication to be assessed who participated at study sites within the scope of SGB V (German Social Security Code) is < 5 per cent of the total number of study participants.

The clinical studies of the medicinal product in the therapeutic indication to be assessed were therefore not conducted to a relevant extent within the scope of SGB V.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 22 January 2026.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 22 January 2026

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken