Gemeinsamer Bundesausschuss

Justification

to the Resolution of the Federal Joint Committee (G-BA) 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

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess the benefit of all reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of rare diseases (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to 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. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 30 million in the last 12 calendar months. According to Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5 Section 5, paragraphs 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decide whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation, the G-BA modified the procedure for the benefit assessment of orphan drugs at their session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determine an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at their session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the turnover threshold according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA must

be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA pass a resolution on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient sepiapterin on 15 July 2025 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 1 VerfO on 15 July 2025.

Sepiapterin for the treatment of hyperphenylalaninaemia in subjects with phenylketonuria is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the approval studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to assess the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 15 October 2025 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA have adopted their resolution on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G12-01) and the statements made in the written statement and oral hearing procedure, as well as the amendment to the benefit assessment drawn up by the G-BA and the addendum prepared by the IQWiG.

In order to determine the extent of the additional benefit, the G-BA have evaluated the studies relevant for the marketing authorisation with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of sepiapterin.

[1] General Methods, version 8.0 from 19.12.2025. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Sepiapterin (Sephience) in accordance with the product information

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 the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

In summary, the additional benefit of sepiapterin is assessed as follows:

For adults and paediatric subjects with phenylketonuria-associated hyperphenylalaninaemia (HPA), there is a hint for a non-quantifiable additional benefit, since the scientific data does not allow quantification.

Justification:

For the assessment of the additional benefit of sepiapterin, the pharmaceutical company submitted the APHENITY study (PTC923-MD-003-PKU or 003 in short) with the dossier. They also submitted the AMPLIPHY study (PTC923-PKU-301 or 301 in short) and the PTC923-MD-004-PKU study (004 in short) for the sub-population of children < 2 years of age as part of the written statement procedure.

APHENITY (study 003)

The APHENITY study is a completed, two-part label-enabling study. In study phase 1, all subjects enrolled were examined for a response to the active ingredient sepiapterin. Phenylalanine (Phe) levels had to be reduced by at least 15% after a 2-week, single-arm, unblinded treatment phase in order to be included in study phase 2. Study phase 2 is a placebo-controlled, double-blind, 6-week study phase. There was a washout phase of 2 to 3 weeks between the two study phases.

Subjects of all ages with clinically diagnosed PKU with hyperphenylalaninaemia (Phe value ≥ 600 µmol/l) were enrolled. In addition, a blood Phe level of ≥ 360 µmol/l had to be present either at one point during the screening or when calculating the average of the last 3 Phe values. If the study participants were still receiving treatment with pegvaliase or BH4 (e.g. sapropterin) during the screening, this therapy had to be discontinued in order to participate in the study.

Only the comparative study phase 2 (RCT) of the APHENITY study was used for the present benefit assessment. In addition to non-responders with a Phe reduction < 15%, children < 2 years with a response to sepiapterin were also excluded from this study phase. These children were able to participate directly in the single-arm long-term extension study 004.

In study phase 2, of the 157 subjects treated in study phase 1, a total of 110 subjects who responded to sepiapterin received either placebo (n = 54) or sepiapterin (n = 56) for 6 weeks.

In the intervention arm, the dosage of sepiapterin was increased starting at 20 mg/kg body weight (BW)/day every 2 weeks up to the on-label dose of 60 mg/kg BW/day. However, this dose titration does not correspond to the requirements in the product information. Overall, data are only available on on-label dosage over the last 2 weeks.

In both study arms, the study participants were to continue their diet with stable Phe intake for the entire duration of the study.

The primary endpoint was the mean change in Phe concentration in the blood from baseline to weeks 5 and 6 (mean value over the two-week period) in phase 2 of the study.

AMPLIPHY (study 301)

The AMPLIPHY study is also a two-part study which investigated the response to sepiapterin in the 2-week single-arm first part of the study. In order to be included in study phase 2, the phenylalanine levels in the blood had to be reduced by at least 20% in contrast to the APHENITY study. Study phase 2 is an actively controlled, open-label, cross-over study phase comparing sepiapterin and sapropterin. Randomisation took place in two sequences, with each study participant receiving both study medications in succession for 4 weeks with a washout phase of 2 weeks. Following the second treatment period, the subjects were able to move on to the long-term extension study 004.

Only the comparative study phase 2 is relevant for the benefit assessment.

Patients with clinically diagnosed PKU with hyperphenylalaninaemia (Phe value ≥ 600 µmol/l) ≥ 2 years were enrolled. In addition, Phe values ≥ 360 µmol/l under the current therapy had to be present at one point during the screening and when calculating the mean value of the last 3 Phe values from the medical history.

Of the 82 subjects treated in study phase 1, a total of 62 subjects with a response to sepiapterin went on to study phase 2, in which they received sapropterin and sepiapterin sequentially.

In the AMPLIPHY study, on-label dose (60 mg/kg BW/day) of sepiapterin was used. In contrast, the dosage of sapropterin differs from the requirements in the product information. The study participants received the maximum dose of 20 mg/kg BW once daily. According to the product information, the dose is usually set in the range of 5 to 20 mg/kg BW/day depending on the Phe values with a starting dose of 10 mg/kg/ BW. In addition, sapropterin is only approved for the treatment of subjects with PKU who have been shown to respond to therapy. However, based on the available data, it is not possible to conclusively assess how many study participants without a response to sapropterin were enrolled.

In both study arms, the study participants were to continue their diet with stable Phe intake for the entire duration of the study.

The primary endpoint was the mean change in blood Phe concentration from baseline to weeks 3 and 4 for each treatment period in study phase part 2.

PTC923-MD-004-PKU

The PTC923-MD-004-PKU study (004 in short) is a single-arm long-term extension (LTE) study on the efficacy and safety of sepiapterin. Among others, subjects from the APHENITY study who were younger than 2 years at the end of part 1 or who had completed part 2 were able to move on to this study. The pharmaceutical company did not present study 004 in the dossier, but subsequently submitted the data for the sub-population of children < 2 years of

age in the written statement procedure. In view of the fact that quantification of the additional benefit for this sub-population cannot be assumed due to the lack of a comparator arm, reassessment of the data was not made.

Limitations of the APHENITY and AMPLIFY studies

The study design of the APHENITY and AMPLIFY studies is subject to relevant uncertainties and limitations. In the comparative study phase 2, only those patients who had already shown a response to treatment with the active ingredient sepiapterin were examined. Thus, the present study population is limited to sepiapterin responders. In addition, there are limitations due to the short observation periods of the comparative study phases of 6 weeks (APHENITY), of which only 2 weeks with administration of on-label sepiapterin dose, and 4 weeks (AMPLIPHY).

Furthermore, the active ingredient sapropterin is only approved for the treatment of subjects with PKU who have been shown to respond to therapy. However, based on the available data, it is not possible to conclusively assess how many study participants without a response to sapropterin were enrolled in the AMPLIPHY study. In addition, no dosage of sapropterin depending on the Phe values was possible in the study; all patients received the maximum dose of 20 mg/kg BW.

Mortality

Fatalities were documented as part of the safety assessment. No deaths occurred during the RCT phase of the APHENITY and AMPLIPHY studies.

Morbidity

Phe concentration in the blood

In the present therapeutic indication, the Phe concentration in the blood is a clinically relevant parameter that is used for diagnosis and therapy management. The "European guidelines on diagnosis and treatment of phenylketonuria"[2] recommend a therapeutic target range for phenylalanine (Phe) in the blood between 120 µmol/l and 360 µmol/l for children up to the age of 12 years. For subjects > 12 years of age with PKU, the target range is between 120 and 600 µmol/l.

Even taking into account the patient-individual variability in clinical manifestation and the limited evidence for the limit value in adults, lowering the Phe concentration in the blood below the limit values in the present therapeutic indication represents a clinical goal in the treatment of patients with phenylketonuria.

Furthermore, the significance of a specific change in the Phe concentration in the blood for the patient-individually pronounced symptomatology is however unclear. The endpoint is therefore not used for the quantification of the additional benefit, but is presented additionally in the resolution.

For both studies, the pharmaceutical company submitted both continuous data on the change in blood Phe levels (primary endpoint) and responder analyses with the threshold values < 600 µmol/l, < 360 µmol/l and < 120 µmol/l.

[2] Van Wegberg AMJ, et al. European guidelines on diagnosis and treatment of phenylketonuria: first revision. Mol Genet Metab 2025;145(2):109125.

However, not all necessary evaluations were currently or subsequently submitted for the threshold values < 360 µmol/l and < 120 µmol/l. On the contrary, the threshold value of < 600 µmol/l is considered inadequate, especially since subjects < 12 years of age represent a relevant part of the study population. The responder analyses are therefore not additionally considered.

In the continuous evaluations of the change in the Phe value at week 5/6 (APHENITY, study phase 2) and at week 3/4 (AMPLIPHY; study phase 2), both studies showed a significant reduction in the Phe value in the sepiapterin arm compared to baseline. There was a statistically significant difference compared to both placebo (APHENITY) and sapropterin (AMPLIPHY).

Natural protein intake

Long-term adherence to a strict phenylalanine-restricted diet with the intake of synthetic amino acid mixtures (to prevent malnutrition) is currently the mainstay of treatment for phenylketonuria. The reduction of phenylalanine levels below the limit values with a simultaneous normalised natural protein intake can therefore be regarded as a therapeutic goal in the present therapeutic indication.

Within the APHENITY and AMPLIPHY studies, the natural protein intake was assessed by the endpoint "estimated daily intake of phenylalanine". However, the endpoint does not allow any conclusion as to whether sepiapterin enables a normal or improved natural protein intake with a simultaneous reduction of the Phe concentration in the blood since the respective protein intake of the study participants should be kept as stable as possible during the entire duration of the study according to the study protocol.

The data for the endpoint "estimated daily intake of phenylalanine" are therefore not presented due to their lack of significance.

General health status (EQ-5D VAS)

In the AMPLIPHY study, the endpoint "general health status" was assessed using the visual analogue scale (VAS) of the European Quality of Life Questionnaire 5 Dimensions (EQ-5D).

However, in contrast to the pre-specified evaluation strategy, the pharmaceutical company only presented the results of the first treatment period. The reason given by the pharmaceutical company is a risk of bias of the second treatment period posed by the first treatment period. However, there are no indications of any carry-over effect. Above all, no baseline characteristics for the study participants were provided for the evaluation of the first treatment period.

Overall, the endpoint is not used for the benefit assessment due to the limitations of the data collection system.

<u>Quality of life</u>

In the AMPLIPHY study, health-related quality of life was assessed using the Phenylketonuria Quality of Life (PKU-QoL) questionnaire. However, the pharmaceutical company did not submit any data on this endpoint, as the study results are unsuitable for assessment of the additional benefit due to the low return rate.

Side effects

In the APHENITY study, the safety data for study phase 2 were collected and evaluated from the day of randomisation for subjects who moved on to LTE 004 until day 42 (week 6). For subjects who did not move on to the LTE, data were collected until day 30 after the last dose.

In the AMPLIPHY study, safety data were collected for study phase 2 from the day of randomisation and for all subjects up to day 14 (+3) of the washout phase of the second treatment period. For subjects who did not move on to LTE, AEs were also assessed by telephone enquiry 30 days after the last dose. Data on the observation period are not available.

In both studies, neither serious adverse events (AEs) nor AEs that led to discontinuation of the study medication occurred in study phase part 2. No severe AEs occurred in the APHENITY study and they occurred in less than 5% of patients in the AMPLIPHY study.

Overall assessment

This assessment is based on the results of the APHENITY study (study 003) and the AMPLIPHY study (study 301). Both studies consist of two study phases. In study phase 1, all subjects enrolled were examined for a response to the active ingredient sepiapterin. Only those subjects who showed a response to the active ingredient sepiapterin were included in study phase 2.

In phase 2 of the APHENITY study, sepiapterin was compared with placebo over a period of 6 weeks.

Study phase 2 of the AMPLIPHY study is an actively controlled, open-label, cross-over study phase comparing sepiapterin and sapropterin. A randomised comparison was carried out in two sequences, with each study participant receiving both study medications in succession for 4 weeks with a washout phase of 2 weeks.

For the present benefit assessment, the results of the comparative study phase 2 (RCT) are used in each case.

Results on mortality and side effects are available. The endpoint of phenylalanine concentration in the blood was also assessed in both studies.

In the assessment of the available study data, it is considered critical that only those patients who had already shown a response to treatment with the active ingredient sepiapterin were examined. Due to this limitation of the study population to sepiapterin responders, the reliability of data is significantly limited. In addition, there are limitations due to the short observation periods of the comparative study phases of 6 weeks (APHENITY), of which only 2 weeks with administration of on-label sepiapterin dose, and 4 weeks (AMPLIPHY).

For the endpoint of phenylalanine concentration in the blood, there was a statistically significant difference in favour of sepiapterin compared to both placebo (APHENITY) and sapropterin (AMPLIPHY). The laboratory parameter has clinical relevance in the diagnosis and monitoring of disease progression, but the significance of a specific change in the phenylalanine concentration in the blood for the patient-individually pronounced symptomatology is unclear.

Overall, the available data are not assessable due to the limitations mentioned and are therefore unsuitable for quantifying the extent of the additional benefit.

The G-BA therefore classify the extent of the additional benefit of sepiapterin for the treatment of adults and paediatric patients with phenylketonuria-associated hyperphenylalaninaemia as non-quantifiable since the scientific data does not allow quantification.

Significance of the evidence

The present assessment is based on the results of the direct comparator study phase of the APHENITY and AMPLIPHY studies.

The significance of the results of the APHENITY study is uncertain, as the dosage of the active ingredient sepiapterin was only administered on-label in the last 2 weeks of the direct comparator study phase.

The risk of bias of the AMPLIPHY study is assessed as high due to the lack of blinding. Furthermore, uncertainties arise due to deviations from the treatment in accordance with the product information (without proven response) and dosage (no individual adjustment according to fixed maximum dose) of the control intervention with sapropterin.

Overall, the significance of the evidence is therefore classified in the "hint" category.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Sephience with the active ingredient sepiapterin.

Sephience was approved as an orphan drug for the treatment of hyperphenylalaninaemia (HPA) in adult and paediatric patients with phenylketonuria (PKU).

The assessment is based on the results of the APHENITY study and the AMPLIPHY study. Each one of the two studies consists of two study phases, whereby the results of the comparator study phase 2 (RCT) are used for the present benefit assessment. In study phase 1, the study participants were examined for a response to sepiapterin in order to include only responders in study phase 2.

In the APHENITY study, sepiapterin was compared with placebo over a period of 6 weeks. The AMPLIPHY study is an actively controlled, open-label, cross-over study phase comparing sepiapterin with sapropterin (4 weeks per sequence).

Results on mortality and side effects are available. The endpoint of phenylalanine concentration in the blood was also assessed in both studies.

In the assessment of the available study data, it is considered critical that only those patients who had already shown a response to treatment with the active ingredient sepiapterin were examined. Due to this limitation of the study population to sepiapterin responders, the reliability of data is significantly limited. In addition, there are limitations due to the short observation periods of the comparative study phases of 6 weeks (APHENITY), of which only 2 weeks with administration of on-label sepiapterin dose, and 4 weeks (AMPLIPHY).

For the endpoint of phenylalanine concentration in the blood, there was a statistically significant difference in favour of sepiapterin compared to both placebo (APHENITY) and sapropterin (AMPLIPHY). The laboratory parameter has clinical relevance in the diagnosis and monitoring of disease progression, but the significance of a specific change in the phenylalanine concentration in the blood for the patient-individually pronounced symptomatology is unclear.

Overall, the available data are not assessable due to the limitations mentioned and are therefore unsuitable for quantifying the extent of the additional benefit. The G-BA therefore classify the extent of the additional benefit of sepiapterin for the treatment of adults and paediatric patients with phenylketonuria-associated hyperphenylalaninaemia as non-quantifiable since the scientific data does not allow quantification. There is a "hint" for the significance of the evidence.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The resolution is based on the information provided by the pharmaceutical company in the benefit assessment dossier. Overall, the specified number of patients in the SHI target population is subject to uncertainty.

To calculate the average annual incidence and prevalence of PKU in Germany, the pharmaceutical company used the data from the national screening reports of the German Society for Neonatal Screening (DGNS), which may lead to an underestimation of the calculated patient numbers. This is partly due to the fact that no information on the underlying limit values of the phenylalanine levels in the blood for the confirmed PKU cases is available for most reporting years, which makes it unclear whether all subjects requiring treatment were included in the calculation.

Uncertainties regarding the stated number of patients in the SHI target population also arise, for example, from the fact that the life expectancy of the general population was used rather than the disease-specific life expectancy. In addition, the SHI routine data analysis used ICD-10 codes, which include both subjects with a different indication and those with mild PKU who do not require pharmacological treatment.

2.3 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.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 November 2025). The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

The (daily) doses recommended in the product information were used as the calculation basis. The active ingredient sepiapterin is administered according to body weight and age. The

resolution therefore indicated a cost range based on the costs for neonates (lower limit) and adults (upper limit).

For children from birth, the average body weight (BW) from the "German Health Interview and Examination Survey for Children and Adolescents (KiGGS)"[3] was used as a basis. For this age group, the reference percentiles of the Robert Koch Institute were used. Based on the average body weights of boys and girls, the average body weight of neonates is 3.46 kg.

For the calculation of dosages depending on body weight of adults, the average body measurements from the official representative statistics “Microcensus 2021 – body measurements of the population”[4] were applied (average body weight: 77.7 kg).

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is different from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

[3] Contributions to Federal Health Reporting. Reference percentiles for anthropometric measures and blood pressure from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS) (2013, both sexes, from birth), https://edoc.rki.de/handle/176904/3254

[4] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Sepiapterin	Continuously, 1 x daily	365.0	1.0	365.0
	Continuously, 1 x daily	365.0	1.0	365.0

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Sepiapterin	26 mg (= 7.5 mg/kg BW)	26 mg	1 x 250 mg	365.0	365 x 250 mg
	4,750 mg (= 60 mg/kg BW)	4,750 mg	4 x 1,000 mg + 3 x 250 mg	365.0	1,460 x 1,000 mg + 1,095 x 250 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Adults and paediatric subjects with phenylketonuria-associated hyperphenylalaninaemia

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Sepiapterin 250 mg	30 POU	€ 3,275.12	€ 1.77	€ 183.75	€ 3,089.60
Sepiapterin 1000 mg	30 POU	€ 12,927.51	€ 1.77	€ 735.00	€ 12,190.74
Abbreviations: POU = powder for oral use					

LAUER-TAXE® last revised: 15 November 2025

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

No additionally required SHI services are taken into account for the cost representation.

2.5 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

According to Section 35a, paragraph 3, sentence 4, the G-BA designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered

due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA have decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA have decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the

assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA have decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section

35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

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.

Justification for the findings on designation in the present resolution:

Adults and paediatric subjects with phenylketonuria-associated hyperphenylalaninaemia

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.

References:

Product information for sepipaterin (Sephience); Sephience™ 250 mg/ 1,000 mg powder for oral use in sachet; last revised: August 2025

2.6 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. In accordance with Section 35a, paragraph 3, sentence 5 SGB V, the G-BA must determine whether a relevant percentage of the clinical studies on the medicinal product were conducted within the scope of SGB V. This is the case if the percentage of study participants who have participated in the clinical studies on the medicinal product to be

assessed in the therapeutic indication to be assessed at study sites within the scope of SGB V is at least five per cent of the total number of study participants.

The calculation is based on all studies that were submitted as part of the benefit assessment dossier in the therapeutic indication to be assessed in accordance with Section 35a, paragraph 1, sentence 3 SGB V in conjunction with Section 4, paragraph 6 AM-NutzenV.

Approval studies include all studies submitted to the regulatory authority in section 2.7.3 (Summary of Clinical Efficacy) and 2.7.4 (Summary of Clinical Safety) of the authorisation dossier in the therapeutic indication for which marketing authorisation has been applied for. In addition, studies, which were conducted in whole or in part within the therapeutic indication described in this document, and in which the company was a sponsor or is otherwise financially involved, must also be indicated.

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 (5.2%) of the total number of study participants according to the information provided by the pharmaceutical company in the dossier. They include the APHENITY and PKU-002 studies in the calculation.

In comparison with the Common Technical Document (CTD), at least 4 further studies with registry entry were identified in the assessment (PKU-001, GAS-001, PBD-001, PTC923-MD-005-HV), which were submitted to the regulatory authority for the assessment of the clinical efficacy and safety of the medicinal product in the therapeutic indication to be assessed. These studies, which did not take place at German study sites, must be included in the calculation of the percentage. As part of the written statement procedure, the pharmaceutical company also submitted data on the AMPLIPHY study, which were taken into account for the recalculation of the percentage of study participants at German study sites.

Taking into account all of the studies mentioned above, the percentage of study participants at German study sites is 2.06%.

The CTD also contains further studies for which no registry entry could be identified. However, according to the CTD, these studies were only carried out in study sites outside Germany and would therefore only lead to a reduction in the percentage value determined.

Against this background, it can be assumed that the percentage of study participants at study sites within the scope of SGB V is less than 5% 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.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

On 15 July 2025, the pharmaceutical company submitted a dossier for the benefit assessment of sepiapterin to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 15 October 2025 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting statements was 5 November 2025.

The oral hearing was held on 24 November 2025.

An amendment to the benefit assessment with a supplementary assessment was submitted on 19 December 2025 and an addendum to the supplementary assessment of the percentage of study participants at study sites within the scope of SGB V was submitted on 18 December 2025.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 13 January 2026, and the draft resolution was approved.

At their session on 22 January 2026, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	10 August 2021	Information of the benefit assessment of the G-BA
Working group Section 35a	18 November 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	24 November 2025	Conduct of the oral hearing
Working group Section 35a	2 December 2025 6 January 2026	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee on Medicinal Products	13 January 2026	Concluding discussion of the draft resolution
Plenum	22 January 2026	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 22 January 2026

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

Prof. Hecken