Gemeinsamer Bundesausschuss

Justification

of 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
Pegzilarginase (hyperargininemia (ARG1-D), ≥ 2 years)

of 4 July 2024

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of 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 German Social Code, Book Five (SGB V). 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 decides 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 its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines 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 its 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 decides 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 pegzilarginase on 15 January 2024 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 12 January 2024.

Pegzilarginase for the treatment of arginase 1 deficiency (ARG1-D), also known as hyperargininemia, in adults, adolescents and children aged 2 years and older 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 of 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 evaluate 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 April 2024 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 has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier assessment carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G24-01) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for the approval 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 pegzilarginase.

1 General Methods, version 7.0 from 19.09.2023. 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 Pegzilarginase (Loargys) in accordance with the product information

Loargys is indicated for the treatment of arginase 1 deficiency (ARG1-D), also known as hyperargininemia, in adults, adolescents and children aged 2 years and older.

Therapeutic indication of the resolution (resolution of 4 July 2024):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

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

For children, adolescents and adults aged 2 years and older with arginase 1 deficiency (hyperargininemia), there is a hint for a non-quantifiable additional benefit of pegzilarginase, since the scientific data does not allow quantification.

Justification:

For the benefit assessment, the pharmaceutical company submits the phase III PEACE study (CAEB1102-300A) in the dossier. This is a randomised, double-blind, multicentre study comparing the efficacy and safety of pegzilarginase (n = 21) versus placebo (n = 11), each in combination with individualised disease management in patients aged 2 years and older with arginase 1 deficiency over 24 weeks.

After completing this controlled phase, the study participants were to move on to the single-arm long-term extension phase of up to 150 weeks. As it is not possible to make a valid interpretation and assessment of the results to derive an additional benefit due to the absence of a control group, only the data from the 24-week randomised controlled phase are used for the present benefit assessment.

The primary endpoint was the change in plasma arginine concentration from baseline to week 24.

Study population

The patients enrolled in the PEACE study were aged between 2 and 29 years. Pegzilarginase has therefore not been studied in middle-aged and elderly subjects with a correspondingly long history of the disease.

The study participants showed a very high arginine concentration. Data on subjects with ARG1-D who have only a moderately high arginine concentration in plasma were not collected due to the inclusion criterion of a value of at least 250 µM.

There were various differences in the baseline characteristics of the patients between the two treatment arms, such as age, arginine concentration, severity of spasticity, walking ability, cognitive delays and muscle spasms. Overall, the control arm appears to have an older population with a more severe disease burden than the intervention arm.

In the placebo arm, a lower percentage of subjects also received a concomitant therapy of nitrogen scavengers. In addition, the dietary requirements were largely met or even undercut

in the pegzilarginase arm, while the requirements were fully met in the placebo arm for large parts of the study.

Mortality

Mortality was collected as part of the safety assessment. No deaths have occurred in the course of the study.

Morbidity

The primary endpoint of the PEACE study was the change in arginine concentration at week 24. In addition, patient-relevant endpoints relating to mobility, adaptive behaviour and health status were collected in the morbidity category. When interpreting the results on morbidity presented in the resolution, it should generally be noted that the patients differed in favour of the intervention arm in terms of key baseline characteristics relating to disease burden, age, individualised disease management and also in the baseline values of the endpoints surveyed. With regard to the endpoints on mobility, the influence of the development-related learning or improvement of motor skills on the endpoints is also unclear, regardless of the study medication. This must be taken into account particularly in view of the fact that the subjects in the placebo arm were older.

Arginine concentration in plasma (primary endpoint)

In the present therapeutic indication, the arginine concentration is a clinically relevant laboratory parameter which is used for diagnosis and therapy management. In patients with ARG1-D, the arginine concentration is usually increased, which results in motor and neurological damage in the patients. Reduction of plasma levels is an important therapeutic goal.

In the PEACE study, there was a significant reduction in arginine concentration after 24 weeks of pegzilarginase administration compared to baseline, while no change was observed with placebo. There is a statistically significant difference between the treatment arms in favour of pegzilarginase.

No valid data could however be identified to show what effect a specific change in arginine concentration has on patient-individual symptomatology. The endpoint is therefore only considered in addition.

2-minute walking test (2MWT)

In the PEACE study, walking ability was recorded as an indicator of the patients' physical performance (endurance) using the 2MWT (walking distance that patients can cover within 2 minutes). The use of a walking aid was permitted during the test.

There was no statistically significant difference between the study arms in the changes in absolute walking distance from baseline to week 24.

Gillette Functional Assessment Questionnaire (GFAQ)

The GFAQ is used to survey independent, maximum functions with the use of aids and ortheses. The questionnaire consists of a "*walking scale*" and a catalogue of questions consisting of 22 items. In the PEACE study, only the 10-step walking scale is used, which measures the patient's usual ability to move with the help of the aids they normally use. A lower value on the scale corresponds to poorer walking ability. The scale was collected by surveying the guardians.

For the present benefit assessment, the continuous analysis of the mean values for the change in GFAQ from baseline to week 24 is used. There was no statistically significant difference between treatment with pegzilarginase or placebo.

Gross Motor Function Measure (GMFM)

The GMFM observation instrument, which was originally developed for children with cerebral palsy, was used to determine gross motor skills. The various tasks it contains are based on the feasibility of a healthy 5-year-old child with normal motor skills and are divided into 5 dimensions (A-E) according to the child's motor development stages. Following a change to the study protocol in the PEACE study, only dimension D with tasks for standing and dimension E with tasks for walking, running and jumping were collected.

In the PEACE study, there was no statistically significant difference between placebo and pegzilarginase for the GMFM of dimension E in the change in gross motor skills from baseline to week 24.

For the change in GMFM-D from baseline to week 24, the pharmaceutical company presented various analyses in the dossier and as part of the written statement procedure. The reason for this is that one subject with a baseline value of 0 was included in the pre-specified main analysis and the effects vary depending on the methodology selected and how this missing baseline value is handled.

The difference is not statistically significant across all analyses. Based on the respective values of Hedges' g, it cannot be concluded that there is a clinically relevant effect for the GMFM-D in the two significant evaluation results.

Functional Mobility Scale (FMS)

Functional mobility was to be determined in the PEACE study using the FMS. The FMS uses a 6-point ordinal scale to record the aids and assistance used for everyday mobility in different environments.

A reduction in mobility caused by hyperargininemia and the associated dependence on mobility aids is generally considered patient-relevant. However, the FMS does not record the disease-specific, but rather the general dependence on means of transport or assistance - without including other direct morbidity and quality of life parameters. This means that it cannot be ruled out that for some patients, for example, development-related learning to walk may lead to an improvement regardless of the study medication or that circumstances independent of the disease, such as a fall or the availability of walking aids, may influence the result.

The endpoint is therefore not used for the benefit assessment.

Vineland Adaptive Behaviour Scales, Second Edition (VABS-II)

The VABS-II endpoint collected in the PEACE study, which measures the ability to cope with the challenges of daily life, is not considered in the benefit assessment due to ambiguities in the operationalisation.

Caregiver Global Impressions of Severity (CaGI-S) and Caregiver Global Impressions of Change (CaGI-C)

The CaGI-S is a questionnaire which, as part of an external assessment by the caregivers, records the impression of the current deficits of the study participants with regard to mobility

aspects, everyday skills, social skills and adaptive behaviour in comparison to other subjects in the same age group without ARG1 deficiency. The endpoint is not used due to unclear validity. The CaGI-C survey, which is intended to collect the caregiver's impression of the change in the quality of mobility aspects, everyday skills, social skills and adaptive behaviour, appears to be more valid than the CaGI-S, but there are no evaluations with adequate effect estimators. Therefore, the endpoint cannot be used for the present benefit assessment.

Quality of life

Paediatric Quality of Life Inventory (PedsQL)

The PedsQL is an established, generic instrument for measuring health-related quality of life, which includes four dimensions (physical, emotional, social and school functioning).

In the PEACE study, the PedsQL was surveyed for patients aged between 2 and 18 years. The survey was based on a self-assessment or on an external assessment by the parents if the subjects were not able to assess themselves or were younger than 5 years. Since a joint evaluation of the external and self-assessment of the PedsQL was not considered appropriate, the pharmaceutical company submitted a separate evaluation of the self-assessment and external assessment as part of the written statement procedure. However, the subsequently submitted analyses are not used for the present benefit assessment. The returns were too low for the external assessment of the PedsQL and, in addition, a *missing completely at random* assumption cannot be made.

The self-assessment is not considered for the benefit assessment due to limitations in validity. For some subjects, external assessments were also available in addition to the self-assessments. There were neither formalised criteria nor documented reasons for the psychological assessment of the ability to self-assess. The classification was made on an individual basis based on the professional expertise of the investigators or the psychologist. It is therefore unclear whether these subjects were able to provide a valid self-assessment and this could not be conclusively clarified during the written statement procedure.

Side effects

In the PEACE study, there was no statistically significant difference between the treatment groups for the endpoints of severe adverse events (AE), serious AEs and discontinuation due to AEs. The AEs that occurred from the 1st dose of the study medication until the end of treatment of the RCT phase at week 24 were taken into account. There were also no significant differences between the study arms in the percentage of subjects with an "AE of special interest" in the categories "Hypersensitivity", "Reaction at the injection site", "Hyperammonaemic episodes" and in the post-hoc-defined AE "Abnormal liver function test" defined by the pharmaceutical company.

Overall assessment

For the present benefit assessment for the treatment of adults, adolescents and children aged 2 years and older with arginase 1 deficiency (hyperargininemia), results of the randomised placebo-controlled pivotal phase III PEACE study over 24 weeks are available.

No deaths occurred in the study.

In the morbidity endpoint category, overall, there were no significant, clinically relevant differences in the patient-relevant endpoints relating to the patients' motor skills (2MWT, GFAQ, GMFM-E). In the GMFM-D endpoint, only two of the five evaluations carried out

showed statistically significant differences in favour of pegzilarginase, but based on the respective values of Hedges' g it cannot be concluded that there is a clinically relevant effect for GMFM-D.

The arginine concentration is a clinically relevant laboratory parameter for diagnosis and therapy management in the present therapeutic indication. There was a statistically significant difference between the treatment arms in the reduction of the arginine concentration in favour of pegzilarginase. No valid data could however be identified to show what effect a specific change in arginine concentration has on patient-individual symptomatology. No relevant differences for the benefit assessment can therefore be derived for morbidity in the overall assessment.

Neither advantages nor disadvantages of pegzilarginase could be observed for the side effects. No suitable data are available for health-related quality of life.

In the overall assessment of the available results on the patient-relevant endpoints, the G-BA classifies the extent of the additional benefit of pegzilarginase for the treatment of arginase 1 deficiency (hyperargininemia) on the basis of the criteria in Section 5, paragraph 8 sentences 1, 2 in conjunction with Section 5, paragraph 5, sentence 1, number 4 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) as non-quantifiable since the scientific data does not allow quantification.

Significance of the evidence

The present benefit assessment of pegzilarginase is based on a randomised controlled phase III PEACE study, which compares pegzilarginase with placebo, each in combination with individualised disease management over 24 weeks.

The study has a high risk of bias between the two treatment arms, particularly due to the unequal distribution in the baseline characteristics and the differences in individualised disease management. The patients in the control arm were older overall and appeared to be more severely ill than those in the intervention arm; in addition, fewer subjects in the placebo arm received nitrogen scavengers as concomitant medicinal therapy. In addition, the dietary requirements were largely met or even undercut in the pegzilarginase arm, while the requirements were fully met in the placebo arm for large parts of the study. Overall, the results may therefore be prone to a risk of bias in favour of pegzilarginase.

Furthermore, the overall reliability of data is limited due to the small sample size due to the rarity of the disease.

The overall analysis gives a hint for an additional benefit with regard to significance of the evidence.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Loargys with the active ingredient pegzilarginase. Loargys received a conditional marketing authorisation as an orphan drug and is indicated for the treatment of arginase 1 deficiency, also known as hyperargininemia, in adults, adolescents and children aged 2 years and older.

The results of the randomised, double-blind, multicentre phase III PEACE study, which compared pegzilarginase with placebo, each in combination with individualised disease management in subjects aged 2 years and older with arginase 1 deficiency (n = 32) over 24 weeks, are available for the benefit assessment.

No deaths occurred in the study.

In the morbidity endpoint category, overall, there were no significant, clinically relevant differences in the patient-relevant endpoints relating to the patients' motor skills (2MWT, GFAQ, GMFM-E). In the GMFM-D endpoint, only two of the five evaluations carried out showed statistically significant differences in favour of pegzilarginase, but based on the respective values of Hedges' g it cannot be concluded that there is a clinically relevant effect for GMFM-D.

The arginine concentration is a clinically relevant laboratory parameter for diagnosis and therapy management in the present therapeutic indication. There was a statistically significant difference between the treatment arms in the reduction of the arginine concentration in favour of pegzilarginase. No valid data could however be identified to show what effect a specific change in arginine concentration has on patient-individual symptomatology. No relevant differences for the benefit assessment can therefore be derived for morbidity in the overall assessment.

Neither advantages nor disadvantages of pegzilarginase could be observed for the side effects. No suitable data are available for health-related quality of life.

The PEACE study is prone to a high risk of bias between the two treatment arms, particularly due to the unequal distribution in the baseline characteristics and the differences in individualised disease management, whereby the results may be biased in favour of pegzilarginase. Furthermore, the overall reliability of data is limited due to the small sample size due to the rarity of the disease.

In the overall assessment, a hint of a non-quantifiable additional benefit.is identified for adults, adolescents and children aged 2 years and older with arginase 1 deficiency (hyperargininemia) since the scientific data does not allow quantification.

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 from the dossier assessment of the IQWiG (mandate G24-01). The pharmaceutical company's data on the number of patients in the SHI target population are however fraught with uncertainty.

This is particularly because information on the percentage values of ethnic groups used to calculate the prevalence of ARG1D in Germany is missing and it is unclear whether the assumed average life expectancy of 40 years is transferable to Germany and whether the frequencies of mutations responsible for ARG1-D are representative.

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 Loargys (active ingredient: pegzilarginase) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 23 May 2024):

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

Treatment with pegzilarginase should only be initiated and monitored by doctors experienced in treating inherited metabolic disorders.

This medicinal product received a conditional marketing authorisation. This means that further evidence of the benefit of the medicinal product is anticipated. The *European Medicines Agency* (EMA) will assess new information on this medicinal product at least annually and update the product information where necessary.

In accordance with the European Medicines Agency requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for patients.

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 June 2024).

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 varies 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.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Pegzilarginase	1 x every 7 days	52.1	1	52.1

Consumption:

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 product information recommends a starting dose of 0.1 mg/kg body weight (BW) per week, which should then be gradually adjusted. For the present cost calculation, a

maintenance dose between 0.05 and 0.2 mg per kg BW is assumed in accordance with the dose range investigated in the approval study[2].

For dosage depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 and 2021 – body measurements of the population" were applied. The average body weight of a 2 to 3-year-old child is 14.1 kg[3] and that of a adults 77.7 kg[4].

The lower range is therefore a dosage of 0.05 mg/kg BW for children aged between 2 and <3 years and the upper range is a dosage of 0.2 mg/kg BW for adults.

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					
Pegzilarginase	0.05 mg/kg BW - 0.2 mg/kg BW	0.7 mg - 15.5 mg	1 x 2 mg - 8 x 2 mg	52.1	52.1 x 2 mg - 416.8 x 2 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 fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

[2] Product information: Loargys 5 mg/ml solution for injection/infusion; Immedica pharma. Last revised 15 December 2023

[3] Federal Health Reporting. Average body measurements of the population (2017, both sexes, 1 year and older), www.gbe-bund.de

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

Costs of the medicinal products:

Adults, adolescents and children aged 2 years and older with arginase 1 deficiency (hyperargininemia)

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					
Pegzilarginase	2 mg	€ 6,718.11	€ 2.00	€ 380.38	€ 6,335.73

LAUER-TAXE® last revised: 15 June 2024

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.

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 designates 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 has 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 has 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 information 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 has 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, adolescents and children aged 2 years and older with arginase 1 deficiency (hyperargininemia)

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

References:

Product information on pegzilarginase (Loargys); Loargys 5 mg/ml solution for injection/infusion; last revised: 15 December 2023

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 12 January 2024, the pharmaceutical company submitted a dossier for the benefit assessment of pegzilarginase 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 April 2024 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 6 May 2024.

The oral hearing was held on 27 May 2024.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the written statement procedure was submitted on 14 June 2024.

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 25 June 2024, and the proposed resolution was approved.

At its session on 4 July 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	9 April 2024	Information of the benefit assessment of the G-BA
Working group Section 35a	14 May 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	27 May 2024	Conduct of the oral hearing
Working group Section 35a	4 June 2024 18 June 2024	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 Medicinal products	25 June 2024	Concluding discussion of the draft resolution
Plenum	4 July 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 4 July 2024

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

Prof. Hecken