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) Pegcetacoplan (new therapeutic indication: paroxysmal nocturnal haemoglobinuria, non-pretreated patients)

of 22 November 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 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 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 active ingredient pegcetacoplan (Aspaveli) was listed for the first time on 1 April 2022 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 6 May 2024, pegcetacoplan received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7).

On 31 May 2024, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient pegcetacoplan with the new therapeutic indication "Treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia and have not received prior therapy with a complement inhibitor" in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

A benefit assessment of pegcetacoplan has already been conducted according to Section 35 a SGB V in the therapeutic indication: "Adults with paroxysmal nocturnal haemoglobinuria who remain anaemic for at least 3 months after treatment with a C5 inhibitor" and in this regard, an amendment to Annex XII was made by resolution of 15 September 2022 (benefit assessment procedure for the active ingredient pegcetacoplan (paroxysmal nocturnal haemoglobinuria, pretreated patients)). This therapeutic indication is not covered by the present benefit assessment. The present benefit assessment refers exclusively to those indications that have been added as a result of the marketing authorisation of the new therapeutic indication.

Pegcetacoplan for the treatment of paroxysmal nocturnal haemoglobinuria is approved as a medicinal product for the treatment of rare diseases 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 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 2 September 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 evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G24-13) 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 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 pegcetacoplan.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Pegcetacoplan (Aspaveli) in accordance with the product information

Aspaveli is indicated as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia.

Therapeutic indication of the resolution (resolution of 22 November 2024):

Aspaveli is indicated as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia and have not received prior therapy with a complement inhibitor.

2.1.2 Extent of the additional benefit and significance of the evidence

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

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

Justification:

The pharmaceutical company has submitted data from the completed, pivotal, multicentre, randomised, controlled, open-label phase III PRINCE study for benefit assessment.

The study was conducted from August 2019 to June 2021 in 22 study sites and 8 countries (Hong Kong, Malaysia, Philippines, Singapore, Thailand, Colombia, Mexico and Peru).

Adults with PNH and haemolytic anaemia, who have not received treatment with a complement inhibitor within three months prior to screening were enrolled. In addition, vaccinations against Neisseria meningitidis types A, C, W, Y and B, Streptococcus pneumoniae and Haemophilus influenzae type B had to have been given within 2 years before the 1st treatment day or within 14 days of starting pegcetacoplan treatment.

The 53 patients were stratified according to the number of transfusions within the last 12 months prior to screening (≤ 4; > 4) and randomised in a 2:1 ratio to the two study arms - pegcetacoplan and standard of care (transfusions, corticosteroids, supplementation).

The study comprised a 4-week screening period, a 26-week randomised controlled (treatment) period (RCP) and an 8-week follow-up (or an open-label extension phase (up to 4 years)).

In addition to the primary study endpoints of stabilisation of the Hb value and change in the LDH value from baseline to week 26, data on symptomatology, health-related quality of life and adverse events were collected.

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

In the dossier, the pharmaceutical company presented the results of the final data cut-off from 5 August 2021, which is used for the present benefit assessment.

On the uncertainties of the PRINCE study

With regard to the PRINCE study, there are relevant uncertainties and limitations in the study design and in the transferability of the study results to the German healthcare context.

From the first treatment day, patients in the comparator arm could receive treatment with pegcetacoplan early if certain criteria were met (crossover). This meant that comparative observation of the fully randomised study population was only possible for approx. 4 weeks. The median time to crossover to treatment with pegcetacoplan was 10.2 weeks. Furthermore, PNH is a chronic disease and treatment with pegcetacoplan is recommended for life according to the product information. As already explained by the G-BA in other resolutions in the therapeutic indication of PNH, a comparative study duration of at least 24 weeks is generally considered necessary here. In this respect, the available results are considered to be insufficiently significant due to the early crossover.

The available data from the PRINCE study are therefore not assessable and thus unsuitable for quantifying the extent of the additional benefit.

Mortality

Overall survival was not collected as a separate endpoint in the PRINCE study. Fatalities were recorded as part of the assessment of the adverse events.

One death occurred in each of the two treatment arms of the study.

Nevertheless, the results for the endpoint category of mortality are not assessable against the background of the uncertainties of the PRINCE study described above and are therefore unsuitable for quantifying the extent of the additional benefit.

Morbidity

Stabilisation of the Hb value until week 26 and change in the LDH value at week 26

The endpoints of *stabilisation of the Hb value and change in the LDH value* were the co-primary endpoints of the PRINCE study.

The endpoints represent laboratory parameters without direct reference to symptoms and are not patient-relevant per se. As these are the co-primary endpoints, they are presented additionally.

Transfusion independence

The endpoint of transfusion independence describes the percentage of patients who did not receive any transfusions (whole blood, red blood cell concentrates or other blood transfusions) during the 26-week treatment period. In the evaluations presented, study participants were classified as transfusion-independent if no transfusion occurred prior to study discontinuation.

Many patients in the present therapeutic indication require periodic transfusions. A long-term or sustainable avoidance of transfusions (transfusion independence or long-term transfusion avoidance) while maintaining a defined minimum value of haemoglobin represents a relevant therapeutic goal in the present therapeutic indication, with which a control of anaemia and anaemia-related symptoms is achieved, while avoiding transfusions. Thus, long-term transfusion independence may represent a patient-relevant endpoint in the present therapeutic indication.

There are uncertainties regarding possible differences in the administration practice of transfusions, as no information can be obtained as to which symptoms were considered transfusion criteria in the PRINCE study and whether these symptoms were predefined.

Nevertheless, the results for transfusion independence are not assessable against the background of the uncertainties of the PRINCE study described above and are therefore unsuitable for quantifying the extent of the additional benefit. Due to limitations in operationalisation and validity, the endpoint is only presented additionally.

Fatigue (FACIT-Fatigue)

In the PRINCE study, fatigue was assessed using the FACIT-Fatigue and the EORTC QLQ-C30 questionnaires.

In the dossier on FACIT-Fatigue, the pharmaceutical company presented evaluations both as continuously scaled variables and in the form of time-to-event analyses. For the benefit assessment, the time-to-event analysis of the time to first deterioration was taken into account. In addition to the manifestation of the fatigue symptomatology, the FACIT-Fatigue also assesses the influence of this symptomatology on functionality in everyday life and social activities.

Nevertheless, the results for FACIT-Fatigue are not assessable against the background of the uncertainties of the PRINCE study described above and are therefore unsuitable for quantifying the extent of the additional benefit.

Symptomatology (EORTC QLQ-C30)

Symptomatology was assessed in the PRINCE study using the symptom scales of the EORTC-QLQ-C30 questionnaire.

The EORTC QLQ-C30 is a generic measurement tool for assessing the symptomatology and quality of life of patients with oncological diseases. The relevance of individual items of the questionnaire for the symptomatology of the present therapeutic indication is unclear. The symptom scales of the EORTC QLQ-C30 are therefore not used for the present assessment.

Nevertheless, the results for symptomatology are not assessable against the background of the uncertainties of the PRINCE study described above and are therefore unsuitable for quantifying the extent of the additional benefit.

Quality of life

EORTC QLQ-C30

Data on health-related quality of life based on the functional scales and the global health status scale of the EORTC QLQ-C30 questionnaire are available for the PRINCE study.

The pharmaceutical company presented evaluations for the time to improvement and deterioration. For the present assessment, the time-to-event analysis for "time to first deterioration" without censoring after a crossover is considered the appropriate analysis against the background of the study design selected here. This is justified, among others, by the fact that a deterioration may occur for relevant PROs before a treatment change and possible improvements in symptomatology or quality of life after a crossover have no influence on the analysis. In addition, more subjects were observed in the "time to first deterioration" time-to-event analyses for a longer period of time than in the "time to first improvement" analyses.

LASA

In the PRINCE study, further data on health-related quality of life was collected using the Linear Analogue Scale Assessment (LASA). Due to the lack of validation of the LASA total score, the individual scales are used for the benefit assessment.

Nevertheless, the results for the endpoint category of quality of life are not assessable against the background of the uncertainties of the PRINCE study described above and are therefore unsuitable for quantifying the extent of the additional benefit.

Side effects

Total adverse events (AEs)

In the PRINCE study, AEs occurred in about 80% of patients in the intervention arm and about 67% of patients in the comparator arm. The results were only presented additionally.

Serious AEs (SAEs), severe AEs

Few severe AEs and SAEs occurred in both treatment arms.

Therapy discontinuation due to AEs

Therapy discontinuation due to AEs did not occur in any of the patient.

Nevertheless, the results for the endpoint category of side effects are not assessable against the background of the uncertainties of the PRINCE study described above and are therefore unsuitable for quantifying the extent of the additional benefit.

Overall assessment

The results of the PRINCE study are available for the benefit assessment of pegcetacoplan for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia. Pegcetacoplan was compared with standard of care (transfusions, corticosteroids, supplementation) during the 26-week, open-label, randomised controlled (treatment) period (RCP) of the study.

With regard to the PRINCE study, there are relevant uncertainties and limitations in the study design and in the transferability of the study results.

From the first treatment day, patients in the comparator arm could receive treatment with pegcetacoplan early if certain criteria were met (crossover). This meant that comparative observation of the fully randomised study population was only possible for approx. 4 weeks. The median time to crossover to treatment with pegcetacoplan was 10.2 weeks. Furthermore, PNH is a chronic disease and treatment with pegcetacoplan is recommended for life according to the product information. As already explained by the G-BA in other resolutions in the therapeutic indication of PNH, a comparative study duration of at least 24 weeks is generally considered necessary here. In this respect, the available results are considered to be insufficiently significant due to the early crossover.

The available data from the PRINCE study are therefore not assessable and thus unsuitable for quantifying the extent of the additional benefit.

In the overall assessment of the available results on the patient-relevant endpoints, the G-BA therefore classifies the extent of the additional benefit of pegcetacoplan for the treatment of adult patients with PNH who have haemolytic anaemia as non-quantifiable on the basis of the criteria in Section 5, paragraph 8 in conjunction with Section 5, paragraph 7, sentence 1, numbers 1 to 4 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) because the scientific data basis does not allow quantification.

Significance of the evidence

The present assessment is based on the results of the randomised, controlled and open-label, phase III PRINCE study.

The risk of bias at the study level is estimated to be high.

There are limitations with regard to the comparator used in the study (standard of care: transfusions, corticosteroids, supplementation). As part of the written statement procedure, the scientific-medical societies state that the comparator used does not reflect the current German standard of care and that patients are treated with C5 inhibitors in the German healthcare context. Furthermore, the EMA describes in the EPAR that the chosen comparator is not optimal in terms of efficacy and safety, as the target population has access to C5 inhibitors.

Patients primarily from Southeast Asia were recruited for the PRINCE study. Studies show that there are differences in the characteristics of Asian and non-Asian patients with PNH as well as indications of a possibly different pathogenesis with regard to haemolysis and its accompanying complications[2]. Against this background, there are uncertainties regarding transferability to the German healthcare context.

In the overall assessment, the uncertainties mentioned with regard to the significance of the evidence result in a hint for an additional benefit.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Aspaveli with the active ingredient pegcetacoplan. Aspaveli was approved as an orphan drug in the following therapeutic indication:

"Aspaveli is indicated as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia."

For the assessment, the pharmaceutical company presented the results of the open-label, randomised, controlled PRINCE study. During the 26-week treatment period, pegcetacoplan was compared with standard of care (transfusions, corticosteroids, supplementation).

In the PRINCE study, there are relevant uncertainties and limitations with regard to the study design and the transferability of the study results.

PNH is a chronic disease. The early crossover meant that comparative observation was only possible for approx. 4 weeks. The median time to crossover to treatment with pegcetacoplan was 10.2 weeks. As already determined by the G-BA in other resolutions in the therapeutic indication of PNH, a comparative study duration of at least 24 weeks is generally considered necessary here. In this respect, the available results are considered to be insufficiently significant due to the early crossover.

The available data from the PRINCE study are therefore not assessable and thus unsuitable for quantifying the extent of the additional benefit.

As a result, a non-quantifiable additional benefit is identified for pegcetacoplan since the scientific data basis does not allow quantification.

[2] Benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V; active ingredient: pegcetacoplan; new therapeutic indication: paroxysmal nocturnal haemoglobinuria, non-pretreated patients; G-BA, date of publication: 2 September 2024

For the significance of the evidence, there are limitations with regard to the comparator, as it does not reflect the current German standard of care. This was explained in the context of the present written statement procedure and in the EPAR.

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 G-BA bases its resolution on the patient numbers from the dossier submitted by the pharmaceutical company. The pharmaceutical company's procedure for deriving the patient numbers is mathematically comprehensible. However, the range is to be assessed as uncertain on the whole. With regard to the lower limit, the information in the routine data analysis are unverifiable and the operationalisation of the percentage of patients via the ICD-10-GM codes used in the routine data analysis is uncertain. There are uncertainties regarding the upper limit, as anaemia is only part of the HDA definition in the analysis of the PNH registry and different haemoglobin thresholds were available in the PNH registry and the APL2-308 approval study.

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 Aspaveli (active ingredient: pegcetacoplan) at the following publicly accessible link (last access: 23 July 2024):

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

Treatment with pegcetacoplan should only be initiated and monitored by specialists who are experienced in the treatment of patients with haematological diseases.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients as well as a patient card. The training material as well as the patient card contain instructions in particular regarding the increased risk of infection with encapsulated bacteria under pegcetacoplan. The patient card should be made available to the patients.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 1 November 2024).

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.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Pegcetacoplan	Continuously, 2 x every 7 days	104.3	1	104.3

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.

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					
Pegcetacoplan	1080 mg	1080 mg	1 x 1080 mg	104.3	104.3 x 1080 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.

Costs of the medicinal products:

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					
Pegcetacoplan	8 INF	€ 30,635.47	€ 2.00	€ 1,749.00	€ 28,884.47
Abbreviations: INF = infusion solution					

LAUER-TAXE® last revised: 1 November 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.

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 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 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 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 with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia and have not received prior therapy with a complement inhibitor

No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

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 31 May 2024, the pharmaceutical company submitted a dossier for the benefit assessment of pegcetacoplan to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

The benefit assessment of the G-BA was published on 2 September 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 23 September 2024.

The oral hearing was held on 7 October 2024.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the written statement procedure was submitted on 29 October 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 12 November 2024, and the draft resolution was approved.

At its session on 22 November 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	27 August 2024	Information of the benefit assessment of the G-BA
Working group Section 35a	17 September 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	7 October 2024	Conduct of the oral hearing
Working group Section 35a	15 October 2024 5 November 2024	Consultation on the dossier evaluation 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	12 November 2024	Concluding discussion of the draft resolution
Plenum	22 November 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 22 November 2024

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

Prof. Hecken