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 Iptacopan (paroxysmal nocturnal haemoglobinuria)

of 19 December 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 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 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 iptacopan on 1 July 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 26 June 2024.

Iptacopan for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia 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 1 October 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 G24-16) 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 iptacopan.

[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 Iptacopan (Fabhalta) in accordance with the product information

Fabhalta 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 19 December 2024):

See the approved therapeutic indication.

2.1.2 Extent of the additional benefit and significance of the evidence

a) Therapy-naive adults with PNH who have haemolytic anaemia

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

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

Justification:

The pharmaceutical company submitted data from the single-arm APPOINT-PNH study for the benefit assessment of the population of therapy-naive adults with PNH who have haemolytic anaemia. In addition, they carry out an indirect comparison in the dossier using a propensity score method against the retrospective APPEX comparator cohort.

APPOINT-PNH study

In addition to the APPLY-PNH study, the APPOINT-PNH study is one of two pivotal studies on iptacopan in this therapeutic indication. The APPOINT-PNH study addresses therapy-naïve adults with PNH who have haemolytic anaemia. This is a completed, multicentre, single-arm phase III study.

Adults with PNH who had a haemoglobin (Hb) value of less than 10 g/dl and a lactate dehydrogenase (LDH) value above one and a half times the upper limit of normal (ULN) were enrolled. In addition, vaccinations against Neisseria meningitidis, Streptococcus pneumoniae and Haemophilus influenzae should have been administered. Patients with a history of previous complement inhibitor treatment, hereditary complement deficiency and haematopoietic stem cell transplantation as well as with proven bone marrow insufficiency (defined as reticulocytes < 100 x 10^9/l, platelets < 30 × 10^9/l and neutrophil granulocytes < 0.5 × 10^9/l) were excluded from enrolment.

The study included an 8-week screening period, a 24-week treatment period and a 24-week extension period.

The primary endpoint of the study was the percentage of patients with an Hb increase by ≥ 2 g/dl with simultaneous transfusion avoidance. Other endpoints on symptomatology, health-related quality of life and adverse events were collected.

The primary analysis was performed pre-specified at week 24 on 2 November 2022 at the end of the treatment phase. Another analysis is carried out pre-specified at week 48 with data cut-off from 18 April 2023 at the end of the extension phase.

On the external comparator cohort APPEX

For the external comparator cohort APPEX, a total of 15 potential registries were initially identified by the pharmaceutical company as part of a literature research and an advisory board. The comparator cohort ultimately included patient-individual data in the form of case reports from the French Registry of Bone Marrow Failure (RIME) and St. James University Hospital Leeds. RIME data is available from 2017 and data from St. James University Hospital Leeds from 2007. Due to the lack of approval by an ethics committee, a registry at Essen University Hospital could not be included in the evaluation. No reasons for exclusion from the other registries were reported.

On the data sources used for APPEX

Overall, only limited information is available on the suitability of the two data sources for formation of the comparator cohort. Both sources differ in terms of the availability of data (e.g. with regard to the parameters "Presence of infection", "Signs and symptoms" and "Relevant medical history and other diseases"). It also remains unclear how many case reports in the databases met the inclusion and exclusion criteria for the base population. A patient pool from the registries used is also not available.

According to the available data, 91 patient-individual records were determined, of which 85 (47 from France and 38 from the United Kingdom (UK)) were included in the comparator cohort. The sample size of 85 required case reports is based on a sample size estimate by the pharmaceutical company, whereby the size of the possible total population or base population remains unclear based on the available data.

Subjects in France were identified through screening, while the sample selection for the comparator population in the UK was based on the screening criteria and random selection. There is no rationale or further explanation for this approach.

Follow-up values were collected irregularly. The times of the laboratory surveys were so heterogeneous that they could not be divided into defined time intervals. In the French data source, laboratory values (including haemoglobin) were collected more frequently than in the UK data source. According to the pharmaceutical company, LDH and reticulocyte values were insufficiently available in both data sources. The collection of baseline values in the retrospective surveys could not be carried out systematically and time points, ratios or local reference intervals could not be adequately collected.

In the overall assessment, it is assumed that the data sources used are not of sufficient quality.

On the derived comparator population APPEX for the indirect comparison

Based on the criteria of the APPOINT-PNH clinical study, the pharmaceutical company applied inclusion and exclusion criteria to the APPEX comparator cohort. In addition to a confirmed diagnosis of PNH, patients had to have an Hb value < 10 g/dl and be treatment-naïve to complement inhibitors. The exclusion criteria included a bone marrow transplant within one year prior to therapy with anti-C5 antibodies, hereditary complement deficiency and a reticulocyte count < 60 $\times 10^9$/l to rule out bone marrow failure.

The inclusion and exclusion criteria of the APPEX comparator cohort therefore differ in part from those of the clinical study. For example, the reason for exclusion of bone marrow failure was operationalised differently and in a simplified manner, and the eligibility threshold with regard to the reticulocyte count was defined differently. Overall, it cannot be ruled out that subjects with bone marrow failure were enrolled in APPEX. However, this is a clear reason for exclusion from the APPOINT-PNH study. An indication of different inclusion and exclusion

criteria in this respect is the presence of myelodysplastic syndrome, which was present in two subjects in the comparator cohort.

In addition, four subjects in APPEX had severe aplastic anaemia at the time of inclusion, while there was no information on this in the APPOINT-PNH study. Furthermore, the inclusion and exclusion criteria used for APPEX do not cover the relevant comorbidities that were specified as exclusion criteria for the APPOINT-PNH clinical study. For example, one subject with existing Budd-Chiari syndrome was enrolled in the APPEX study, which represents a severe liver disease with an increased risk of thrombosis and was a reason for exclusion from the APPOINT-PNH study. According to the information provided by the pharmaceutical company, no information on kidney disease, glomerular filtration rate or creatinine was available in the data sources. Due to the lack of data availability, an underestimation of relevant but uncollected comorbidities cannot be ruled out.

The differences in the inclusion and exclusion criteria are associated with a high risk of selection bias and potentially result in systematically different populations for the indirect comparison. Furthermore, there are systematic differences in the data collection time points between the populations/ study arms to be compared. This makes comparability even more difficult, as it is unclear whether treatment was started at a comparable stage of the disease (different "time zero"). The lack of simultaneity leads to further uncertainties.

The APPEX study also includes retrospective case reports from subjects in Europe. However, the majority of participants in the APPOINT-PNH study came from Asia and 50% of them belonged to a Chinese population. Based on the available documents, it cannot be ruled out that there may be structural differences in the baseline characteristics and in the initiation of treatment in everyday care between the Asian and European populations. This can have an impact on positivity.

About the methodology of the indirect comparison

To identify confounders, the pharmaceutical company conducted a systematic literature review for guidelines, systematic reviews and observational studies in the therapeutic indication, thereby identifying 37 sources. In addition, the identified confounders were classified by experts and the principal investigator. Conducting a systematic literature research and a subsequent survey to classify the confounders according to relevance is considered appropriate overall.

However, the procedure for classifying and agreeing on the relevance of the confounders is incomprehensible on the basis of the available documents and does not ensure an assessment of relevance - independent of data availability - due to the selection by experts. Several confounders that have frequently been identified as relevant in guidelines were classified as "unimportant" in the expert consultation. The majority of the confounders classified as "very important" or "important" were not included in the propensity score model. The operationalisation of aplastic anaemia/ neutropenia/ bone marrow failure from three different confounders to one composite confounder is questionable. The "kidney disease" confounder, which was identified as important, could not be included in the model due to limited data availability. According to the pharmaceutical company, "age" and "sex" were included in the model as perturbation variables to prevent unmeasured confounding. The "performance status" confounder identified as "very important" was also not included in the model.

Based on the study documents submitted with regard to the relevance of the confounders, a selection of confounders driven by data availability cannot be ruled out. The selection of the

confounders used for the propensity score model for the main analysis is assessed as incomplete and therefore unsuitable.

With regard to the statistical methodology, the pharmaceutical company chooses the adjustment method to be an Augmented Inverse Probability Weighting (AIPW) with an Average Treatment Effect on the Treated (ATT) estimator as the "Target of inference". However, this no longer refers to the total derived comparator population, but to a constructed population that cannot be clearly described. The limitations mentioned, particularly with regard to the completeness of the confounders, positivity and "time zero", also mean that the calculated effect estimator cannot be meaningfully interpreted for statements on efficacy.

In addition, no distribution of propensity scores was presented, which is why the overlap of the study populations is unclear. Therefore, it cannot be conclusively assessed to what extent the pseudopopulation generated differ from the total population and whether the results for the pseudopopulation can be transferred to the total population.

The statistical methods used by the pharmaceutical company to calculate the propensity scores sometimes require very strong assumptions to be made about the data basis. However, the lack of consideration of relevant confounders and their limited comparability with regard to "time zero" as well as the unillustrated positivity cannot be compensated for by complex statistical methods with unfounded decision structures for model selection. Based on the available documents, the submitted analyses lead to the model that best fits the present data basis and the decision structure used. A data-driven model selection cannot be ruled out on the basis of the available documents.

The indirect comparison presented also only looks at a selection of endpoints. No comparative analyses are available for patient-reported endpoints and adverse events.

Conclusion on the indirect comparison presented

In the overall assessment, the limited availability of data, the unclear structural equality and comparability of the population of the APPOINT-PNH study with the external comparator cohort APPEX and the inadequate confounder adjustment using the propensity score methods used mean that the propensity score method used is assessed as invalid and the resulting effect estimators as incomprehensible. The indirect comparison presented is therefore not used for the present benefit assessment.

About the results of the APPOINT-PNH study

Mortality

Overall survival was not collected as a separate endpoint in the APPOINT-PNH study. Fatalities were recorded as part of the assessment of the adverse events. No death occurred during the entire study duration.

Due to the single-arm study design, a comparative assessment of overall survival is not possible.

Morbidity

Haemoglobin value-associated endpoint

The primary endpoint of the study was an increase in the Hb value by ≥ 2 g/dl with simultaneous transfusion independence.

The endpoint represents a laboratory parameter without direct reference to symptoms and is not patient-relevant per se. As this is the primary endpoint, it is presented additionally.

Transfusion independence

The endpoint of transfusion independence was defined as the percentage of subjects who did not receive a transfusion of red blood cell concentrate (RBC) between week 2 and week 24 or week 48 and who did not meet any of the following transfusion requirement criteria:

- haemoglobin (Hb) value > 7 and ≤ 9 g/dl (> 6 and ≤ 8 g/dl for the Chinese population) and presence of symptomatic transfusion criteria with sufficient severity to justify transfusion.
- Hb value < 7 g/dl (≤ 6 g/dl for the Chinese population) regardless of the occurrence of the symptomatic transfusion criteria.

Patients who met the transfusion criteria specified in the study protocol were categorised as transfused, regardless of whether a transfusion was administered. Subjects were therefore categorised as non-responders ("transfused") if they fulfilled the transfusion criteria but did not actually receive a transfusion.

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.

With regard to the operationalisation described above, there are uncertainties in that the reasons for the different transfusion criteria for the Chinese population remain unclear and it is not clear why the survey only begins on day 14. The start on day 14 is viewed critically overall as preceding events are not taken into account. Therefore, in the present case, the evaluations from day 1 to week 48 are used for patients who actually received a transfusion. Here, 85% of patients show transfusion independence.

Due to the single-arm study design, a comparative assessment of the data is not possible.

Breakthrough haemolysis

The endpoint of breakthrough haemolysis was defined in the APPOINT-PNH study as:

- lactate dehydrogenase (LDH) value > 1.5 × ULN and increase in LDH value compared to the last two measurements
  AND
- presence of at least one of the following clinical criteria:

    o massive haemoglobinuria, pain crisis, dysphagia or other clinical signs or symptoms associated with PNH OR

    o decrease in the Hb value by ≥ 2 g/dl compared to the previous measurement or a measurement within the last 15 days.

Breakthrough haemolysis could therefore be based exclusively on laboratory parameters (LDH and Hb) without clinically relevant symptoms occurring. However, the two breakthrough haemolyses that occurred in the APPOINT-PNH study exclusively included symptomatic patients.

In principle, symptoms associated with breakthrough haemolysis are patient-relevant. In the present case, the final assessment of the presence of breakthrough haemolysis was made by the principal investigators. In this regard, it remains unclear whether all individual symptoms that can occur in the context of breakthrough haemolysis have been fully collected by the operationalisation. With regard to the component "or other clinical signs or symptoms associated with PNH", it also remains unclear which specific events could have been included in the collection of the endpoint and whether this ensures complete collection of patient-relevant events.

Due to the uncertainties described, the endpoint of breakthrough haemolysis is not considered patient-relevant in the present case and is only presented additionally.

Fatigue (FACIT-Fatigue and Patient Global Impression of Severity (PGIS))

In the APPOINT-PNH study, the fatigue perceived by the patients was assessed using the FACIT-Fatigue and PGIS.

The results are comparable in terms of order of magnitude. An improvement in the FACIT-Fatigue score was achieved by 55% of patients, while the value for the PGIS was 60%.

Due to the single-arm study design, a comparative assessment of the data is not possible.

Symptomatology (EORTC QLQ-C30)

Data on symptomatology was collected 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.

General health status (EQ-5D, visual analogue scale)

The health status of the patients was assessed in the APPOINT-PNH study using the visual analogue scale (VAS) of the EQ-5D questionnaire. An improvement was observed in 50% of patients.

Due to the single-arm study design, a comparative assessment of the data is not possible.

Major adverse vascular events (MAVE)

No serious adverse vascular event occurred during the entire study duration.

Due to the single-arm study design, a comparative assessment of the data is not possible.

Quality of life

Data on health-related quality of life from the APPOINT-PNH study are available using the functional scales and the global health status scale of the EORTC QLQ-C30 questionnaire.

The individual scales showed improvements in the range of 32.5% to 75% of patients.

Due to the single-arm study design, a comparative assessment of the data is not possible.

Side effects

Adverse events (AEs) in total

AEs occurred in just over 90% of patients. The results were only presented additionally.

Serious AEs (SAEs), severe AEs and therapy discontinuation due to AEs

SAEs occurred in 20% and severe AEs in 10% of patients. There was no therapy discontinuation due to AEs in the APPOINT-PNH study.

Specific AEs

In detail, the results on SAEs and severe AEs (CTCAE grade ≥ 3) at system organ class (SOC) level and AEs of special interest, which are observed with an incidence > 10% in at least one study arm, show in particular that infections occur at an order of magnitude of just over 10%.

Due to the single-arm study design, a comparative assessment of side effects is not possible.

Overall assessment

For the benefit assessment of iptacopan as monotherapy, results from the completed, multicentre, single-arm phase III APPOINT-PNH study on mortality, morbidity, quality of life and side effects are available for the population of therapy-naive adults with PNH who have haemolytic anaemia.

In addition, the pharmaceutical company presented an indirect comparison of these data with the retrospective comparator cohort APPEX in the dossier.

The indirect comparison presented is assessed as invalid due to the limited availability of data, the unclear structural equality and comparability of the APPOINT-PNH study population with the external comparator cohort APPEX and the insufficient confounder adjustment by means of the propensity score methods used. The indirect comparison is therefore not used for the present benefit assessment.

No statement on the extent of the additional benefit can be made on the basis of the study results due to the single-arm study design of the APPOINT-PNH study.

In the overall assessment, the G-BA classifies the extent of the additional benefit of iptacopan as monotherapy for the treatment of therapy-naive adults with PNH who have haemolytic anaemia as non-quantifiable since the scientific data does not allow quantification.

Significance of the evidence

The benefit assessment is based on the data of the single-arm pivotal study APPOINT-PNH. Due to the single-arm study design, a comparative assessment is not possible and no statement on the extent of the additional benefit can be made on the basis of the study results.

In the overall assessment, this results in the classification of the significance of the evidence in the “hint" category.

b) Pretreated adults with PNH who have haemolytic anaemia

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

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

Justification:

For the population of pretreated adults with PNH who have haemolytic anemia, the pharmaceutical company has submitted data from the APPLY-PNH study.

In addition to the APPOINT-PNH study, the APPLY-PNH study is one of two pivotal studies on iptacopan in this therapeutic indication. The APPLY-PNH study addresses pretreated adults with PNH who have haemolytic anaemia. This is a completed, multicentre, open-label, randomised-controlled phase III study.

Adults with PNH who had a haemoglobin (Hb) level below 10 g/dL and had been on stable treatment with an anti-C5 antibody (ravulizumab or eculizumab) for at least six months were enrolled. In addition, vaccinations against Neisseria meningitidis, Streptococcus pneumoniae and Haemophilus influenzae should have been administered. Patients with hereditary complement deficiency and a history of haematopoietic stem cell transplantation as well as proven bone marrow insufficiency (defined as reticulocytes < 100 × 109/l, platelets < 30 × 109/l and neutrophil granulocytes < 0.5 × 109/l) were excluded from enrolment.

The study included a 8-week screening period, a 24-week randomised-controlled treatment period (RCP) and a 24-week extension period in which all patients received iptacopan. For the RCP, patients were randomised into the intervention arm (iptacopan; N = 62) and the control arm (continuation of ravulizumab or eculizumab; N = 35) stratified by previous anti-C5 antibody (eculizumab vs ravulizumab) and transfusion history in the last six months prior to randomisation (transfusion received vs no transfusion received).

The co-primary endpoints of the study were the percentage of patients with an Hb increase by ≥ 2 g/dl with simultaneous transfusion avoidance and the percentage of patients with an Hb increase to ≥ 12 g/dl with simultaneous transfusion avoidance. Other endpoints on symptomatology, health-related quality of life and adverse events were collected.

The primary analysis was performed pre-specified at week 24 on 26 September 2022 at the end of the RCP. The final analysis was performed prespecified at week 48 with data cut-off on 6 March 2023 at the end of the extension period.

Mortality

Overall survival was not collected as a separate endpoint in the APPLY-PNH study. Fatalities were recorded as part of the assessment of the adverse events. No death occurred during the entire study duration.

Morbidity

Haemoglobin value-associated endpoints

Co-primary endpoints of the study were an increase in the Hb value by ≥ 2 g/dl and to ≥ 12 g/dl with simultaneous transfusion independence.

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 was defined as the percentage of subjects who did not receive a transfusion of red blood cell concentrate (RBC) between week 2 and week 24 of the RCP or who did not meet any of the following transfusion requirement criteria:

- Haemoglobin (Hb) value ≤ 9 g/dl in the presence of clinical signs or symptoms of a severity that justifies transfusion.
- Hb value ≤ 7 g/dl regardless of the presence of clinical signs or symptoms.

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.

With regard to the operationalisation described above, there are uncertainties in that the start of the survey at week 2 is viewed critically overall as preceding events are not taken into account. In addition, patients who met the transfusion criteria specified in the study protocol were categorised as transfused, regardless of whether a transfusion was administered. Subjects were therefore categorised as non-responders ("transfused") if they fulfilled the transfusion criteria but did not actually receive a transfusion.

In this regard, the pharmaceutical company subsequently submitted further analyses on the endpoint of transfusion independence with their written statement, of which the evaluations from day 1 to week 24 on patients who actually received a transfusion with concomitant symptomatology are used in the present case.

There was a statistically significant difference to the advantage of iptacopan in this case.

Breakthrough haemolysis

The endpoint of breakthrough haemolysis was defined in the APPLY-PNH study as:

- lactate dehydrogenase (LDH) value > 1.5 × ULN and increase in LDH value compared to the last two measurements
  AND
- presence of at least one of the following clinical criteria:

  o massive haemoglobinuria, pain crisis, dysphagia or other clinical signs or symptoms associated with PNH OR

  o decrease in the Hb value by ≥ 2 g/dl compared to the previous measurement or a measurement within the last 15 days.

Breakthrough haemolysis could therefore be based exclusively on laboratory parameters (LDH and Hb) without clinically relevant symptoms occurring. With their written statement, the pharmaceutical company submitted further analyses on the endpoint of breakthrough haemolysis which only included symptomatic patients.

In principle, symptoms associated with breakthrough haemolysis are patient-relevant. In the present case, the final assessment of the presence of breakthrough haemolysis was made by the principal investigators. In this regard, it remains unclear whether all individual symptoms that can occur in the context of breakthrough haemolysis have been fully collected by the operationalisation. With regard to the component "or other clinical signs or symptoms associated with PNH", it also remains unclear which specific events have been included in the collection of the endpoint and whether this ensures complete collection of patient-relevant events.

Due to the uncertainties described, the endpoint of breakthrough haemolysis is not considered patient-relevant in the present case and is only presented additionally.

Fatigue (FACIT-Fatigue and Patient Global Impression of Severity (PGIS))

In the APPLY-PNH study, the fatigue perceived by the patients was assessed using the FACIT-Fatigue and PGIS.

The results for each of the two measurement instruments showed a statistically significant advantage of iptacopan.

Symptomatology (EORTC QLQ-C30)

Data on symptomatology was collected using the symptom scales of the EORTC QLQ-C30 questionnaire, but not used for the present assessment for the reasons mentioned above.

General health status (EQ-5D, visual analogue scale)

The health status of the patients was assessed in the APPLY-PNH study using the visual analogue scale (VAS) of the EQ-5D questionnaire. There was a statistically significant difference to the advantage of iptacopan.

Major adverse vascular events (MAVE)

For severe adverse vascular events, there was no statistically significant difference between the study arms.

The overall assessment of the morbidity results showed advantages in the endpoint of transfusion independence, with regard to the fatigue symptom and the general health status, which are assessed overall as a significant improvement in morbidity.

Quality of life

Data on health-related quality of life from the APPLY-PNH study are available using the functional scales and the global health status scale of the EORTC QLQ-C30 questionnaire.

There were statistically significant advantages of iptacopan in the scales for physical functioning, role functioning, social functioning and global health status, which are assessed overall as a significant improvement in quality of life.

Side effects

Adverse events (AEs) in total

AEs occurred in around 80% of patients in each of the study arms. The results were only presented additionally.

Serious AEs (SAEs), severe AEs and therapy discontinuation due to AEs

There were no statistically significant differences between the treatment arms for the endpoints of SAEs, severe AEs and therapy discontinuation due to AEs.

Specific AEs

In detail, there were no statistically significant differences in the results for SAEs and severe AEs (CTCAE grade ≥ 3) that occurred with an incidence > 5% at system organ class (SOC) or preferred term (PT) level or for AEs of special interest.

Overall assessment

For the benefit assessment of iptacopan as monotherapy, results from the completed, multicentre, open-label, randomised-controlled phase III APPLY-PNH study on mortality, morbidity, quality of life and side effects are available for the population of pretreated adults with PNH who have haemolytic anaemia. In the study, iptacopan was compared with continued therapy with eculizumab or ravulizumab.

With regard to mortality, no deaths occurred in the APPLY-PNH study.

In the morbidity endpoint category, there were advantages with regard to the endpoint of transfusion independence, the fatigue symptom and the general health status, which were assessed overall as a significant improvement in morbidity.

In terms of health-related quality of life, there were advantages in physical functioning, role functioning, emotional functioning and global health status, which are assessed overall as a significant improvement in health-related quality of life.

In terms of side effects, neither advantages nor disadvantages of iptacopan compared to ravulizumab or eculizumab can be derived.

In the overall assessment, limited transferability of the results of the APPLY-PNH study to the German healthcare context is assumed during quantification of the extent of the additional benefit based on the clear advantages of iptacopan compared to continued treatment with eculizumab or ravulizumab (C5 complement inhibitors). This is based on the fact that the current standard of care for patients with clinically significant extravascular haemolysis, characterised in particular by persistent anaemia, reticulocytosis and existing symptomatology, is to switch therapy to proximal complement inhibition (C3 complement inhibitors) instead of continuing terminal complement inhibition (C5 complement inhibitors), particularly taking into account the statements of clinical experts in the written statement procedure. In this regard, the APPLY-PNH study included anaemic patients with an Hb value below 10 g/dl, of whom around 63% of patients in the intervention arm and around 69% of patients in the comparator arm showed PNH-associated symptoms at baseline. Over half of the patients in both study arms also had a transfusion history in the last 6 months prior to randomisation. The median reticulocyte count at baseline was over 150 x 10^9 cells per litre in both study arms.

It can therefore be assumed that the unchanged continuation of treatment with ravulizumab or eculizumab does not reflect the current German standard of care for a large proportion of patients in the APPLY-PNH study. Due to this relevant limitation, the extent of the additional benefit cannot be quantified with sufficient certainty in the overall assessment of the present results. The advantages of iptacopan compared to continued therapy with eculizumab or ravulizumab were assessed here as significant improvements in terms of morbidity and health-related quality of life.

In the overall assessment, the G-BA classifies the extent of the additional benefit of iptacopan as monotherapy for the treatment of pretreated adults with PNH who have haemolytic anaemia 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 open-label, randomised-controlled phase III APPLY-PNH study.

Due to the open-label study design, the risk of bias is assessed as high at study level and at endpoint level, particularly with regard to the patient-reported endpoints.

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 Fabhalta with the active ingredient iptacopan.

Iptacopan was approved as an orphan drug in the following therapeutic indication:

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

The marketing authorisation is based on the APPOINT-PNH and APPLY-PNH studies, resulting in the following patient groups:

a) therapy-naive adults with PNH who have haemolytic anaemia

and

b) pretreated adults with PNH who have haemolytic anaemia.

On patient group a)

For patient group a), results are available from the completed, multicentre, single-arm phase III APPOINT-PNH study on mortality, morbidity, quality of life and side effects.

In addition, the pharmaceutical company presented an indirect comparison of these data with the retrospective comparator cohort APPEX in the dossier.

The indirect comparison presented is assessed as invalid and accordingly not used due to the limited availability of data, the unclear structural equality and comparability of the APPOINT-PNH study population with the external comparator cohort APPEX and the insufficient confounder adjustment by means of the propensity score methods used.

No statement on the extent of the additional benefit can be made on the basis of the study results due to the single-arm study design of the APPOINT-PNH study.

In the overall assessment, the G-BA classifies the extent of the additional benefit as non-quantifiable since the scientific data does not allow quantification.

No statement on the extent of the additional benefit can be made on the basis of the study results due to the single-arm study design. The significance of the evidence is classified in the "hint" category.

On patient group b)

For patient group b), results are available from the completed, multicentre, open-label, randomised-controlled phase III APPLY-PNH study on mortality, morbidity, quality of life and side effects. In the study, iptacopan was compared with continued therapy with eculizumab or ravulizumab.

With regard to mortality, no deaths occurred in the APPLY-PNH study.

In the morbidity endpoint category, there were advantages in terms of transfusion independence, the fatigue symptom and general health status, which were assessed overall as a significant improvement in morbidity.

There was also a significant improvement overall in health-related quality of life.

In terms of side effects, neither advantages nor disadvantages of iptacopan compared to ravulizumab or eculizumab can be derived.

Due to the fact that it can be assumed that the unchanged continued treatment with ravulizumab or eculizumab does not reflect the current German standard of care for a large proportion of patients in the APPLY-PNH study, there is a relevant limitation with regard to the transferability of the results of the APPLY-PNH study to the German healthcare context, which is why, in the overall assessment, the G-BA identified a non-quantifiable additional benefit based on the clear advantages of iptacopan compared to continued treatment with

eculizumab or ravulizumab with regard to improvement in morbidity and health-related quality of life.

The significance of the evidence is classified in the "hint" category especially due to the open-label study design.

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 pharmaceutical company's derivation of the patient numbers in the dossier is mathematically mostly comprehensible but subject to uncertainty. This lies, for example, in the fact that the pharmaceutical company implicitly assumes in their approach that all complement inhibitor-pretreated patients continue to have haemolytic anaemia and in the fact that haemolytic anaemia in complement inhibitor-naïve patients was operationalised via the presence of high disease activity in the lower limit.

In view of these uncertainties, the information from the resolutions on pegcetacoplan of 22 November 2024 and 15 September 2022 are used as a basis for the present resolution in order to enable a consistent consideration of the patient numbers, taking into account the most recent resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the therapeutic indication in question.

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 Fabhalta (active ingredient: iptacopan) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 20 November 2024):

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

Treatment with iptacopan 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 iptacopan. The training material also contains instructions regarding the risk of severe haemolysis after discontinuation of iptacopan. 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 December 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				
Iptacopan	Continuously, 2 x daily	365	1	365.0

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.

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					
Iptacopan	200 mg	400 mg	2 x 200 mg	365	730 x 200 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:

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					
Iptacopan	3 x 56 HC	€ 112,400.99	€ 2.00	€ 6,418.65	€ 105,980.34
Abbreviations: HC = hard capsules					

LAUER-TAXE® last revised: 1 December 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.

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1 October 2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic agents a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

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:

a) Therapy-naive adults with PNH who have haemolytic anaemia

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.

b) Pretreated adults with PNH who have haemolytic anaemia

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 26 June 2024, the pharmaceutical company submitted a dossier for the benefit assessment of iptacopan 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 1 October 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 22 October 2024.

The oral hearing was held on 11 November 2024.

An amendment to the benefit assessment with a supplementary assessment was submitted on 28 November 2024.

A new version of the G-BA's dossier assessment for pretreated patients was prepared on 7 October 2024. This version 1.1 of 7 October 2024 replaces version 1.0 of the dossier assessment of 1 October 2024 and was brought to the attention of the Subcommittee on Medicinal Products at its session on 29 October 2024. The assessment result was not affected by the changes in version 1.1 compared to version 1.0.

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 10 December 2024, and the draft resolution was approved.

At its session on 19 December 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	24 September 2024	Information of the benefit assessment of the G-BA
Working group Section 35a	5 November 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	11 November 2024	Conduct of the oral hearing
Working group Section 35a	19 November 2024 3 December 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	10 December 2024	Concluding discussion of the draft resolution
Plenum	19 December 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 19 December 2024

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

Prof. Hecken