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
Crovalimab (paroxysmal nocturnal haemoglobinuria, ≥ 12 years, ≥ 40 kg)

of 6 March 2025

Contents

Courtesy translation – only the German version is legally binding.

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. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment 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 crovalimab on 15 October 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 13 September 2024.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 16 December 2024 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of crovalimab compared with the appropriate comparator therapy could be determined on the basis of the dossier of the

Courtesy translation – only the German version is legally binding.

pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure, as well of the addendum drawn up by the IQWiG on the benefit assessment. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of crovalimab.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Crovalimab (Piasky) in accordance with the product information

Piasky as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH):

- In patients with haemolysis with clinical symptom(s) indicative of high disease activity.
- In patients who are clinically stable after having been treated with a complement component 5 (C5) inhibitor for at least the past 6 months.

Therapeutic indication of the resolution (resolution of 06.03.2025):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH) and haemolysis with clinical symptom(s) indicative of high disease activity

Appropriate comparator therapy:

Eculizumab or ravulizumab

b) Adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH) who have been receiving a C5 inhibitor for ≥ 6 months and are clinically stable

Appropriate comparator therapy:

Eculizumab or ravulizumab

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

Courtesy translation – only the German version is legally binding.

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application, unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Courtesy translation – only the German version is legally binding.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

On 1. In addition to crovalimab, the active ingredients eculizumab, ravulizumab, pegcetacoplan, danicopan and iptacopan are available for the treatment of PNH based on their authorisation status.

On 2. It is assumed that an allogeneic stem cell transplantation is not indicated at the time of therapy with crovalimab. Accordingly, a non-medicinal treatment cannot be considered as an appropriate comparator therapy for crovalimab in this therapeutic indication.

On 3. For the present therapeutic indication, the following resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V are available:

- Iptacopan: resolution of 19 December 2024
- Danicopan: resolution of 22 November 2024
- Pegcetacoplan: resolutions of 15 September 2022 and 22 November 2024
- Ravulizumab: resolutions of 6 February 2020 and 18 March 2022

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V. There is a joint written statement of the German Society for Haematology and Medical Oncology (DGHO), the Society for Paediatric Oncology and Haematology (GPOH) and the Society for Thrombosis and Haemostasis Research (GTH).

Among the approved active ingredients listed under 1., only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of care.

The evidence in the present therapeutic indication is very limited. Only one systematic review by Zhou et al (2021) that discusses the therapeutic significance of eculizumab in the treatment of PNH could be identified. The authors conclude that eculizumab can reduce the transfusion rate, but further safety studies are needed. Cochrane reviews or relevant guidelines could not be identified.

The therapeutic indication of crovalimab results in two distinct treatment settings, each with a different therapeutic goal in each case: On the one hand, the treatment of haemolysis with clinical symptom(s) indicative of high disease activity, on the other, the maintenance of a clinically stable state achieved under a prior therapy with

Courtesy translation – only the German version is legally binding.

a C5 inhibitor. The G-BA considers it appropriate to divide patients into two patient groups depending on the therapeutic goal.

a) Adult and paediatric patients with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH) and haemolysis with clinical symptom(s) indicative of high disease activity

For patient group a), it is assumed that only patients with PNH and clinical symptoms of haemolysis requiring treatment are covered by this therapeutic indication. Patients with concomitant bone marrow failure – also in the context of aplastic anaemia – are not further considered here.

The terminal complement inhibitors eculizumab and ravulizumab, which are directed against the complement component C5, are available for the treatment of children and adults with PNH. In addition, the proximal complement inhibitors pegcetacoplan and iptacopan as well as danicopan are approved as add-on therapy to ravulizumab or eculizumab for adults with PNH who have haemolytic anaemia.

In their written statement on the present benefit assessment, the scientific-medical societies named the proximal complement inhibitors pegcetacoplan and iptacopan as the therapy standard for untreated patients with PNH in addition to the C5 complement inhibitors ravulizumab and eculizumab.

By resolution of 6 February 2020, the G-BA did not identify any additional benefit of ravulizumab for the treatment of adult patients with PNH compared to the appropriate comparator therapy eculizumab as there were neither positive nor negative effects. By resolution of 18 March 2022, no additional benefit over the appropriate comparator therapy eculizumab was identified for paediatric patients as no assessable data were presented.

With regard to patients who continue to be symptomatic despite treatment with a C5 inhibitor, the continuation of inadequate therapy with existing optimisation options does not represent the appropriate comparator therapy. It is assumed that any dose adjustments in the form of an adjustment of the dose interval during treatment with eculizumab or ravulizumab will be made if necessary.

With regard to the proximal complement inhibitors pegcetacoplan and iptacopan, the clinical experts stated in the oral hearing that it is common practice to initially use a terminal complement inhibitor in first-line therapy and to switch to a proximal inhibitor in the presence of significant extravascular haemolysis due to the limited clinical experience with this substance class in healthcare.

According to the statements made by the experts at the oral hearing, a change from terminal to proximal complement inhibition is required in the event of significant extravascular haemolysis. It is therefore assumed that further exclusively terminal complement inhibition with crovalimab is not generally indicated in this treatment setting.

Accordingly, the proximal complement inhibitors pegcetacoplan and iptacopan do not represent an appropriate comparator therapy for crovalimab.

Courtesy translation – only the German version is legally binding.

The proximal complement inhibitor danicopan is approved as an add-on therapy to ravulizumab or eculizumab for adults with PNH who have residual haemolytic anaemia.

By resolution of 22 November 2024, the G-BA identified a hint for a non-quantifiable additional benefit of danicopan in this therapeutic indication since the scientific data did not allow quantification.

Neither in their written statement nor during the oral hearing, the scientific-medical societies mention danicopan as a relevant therapy option in the present therapeutic indication. This is still a relatively new treatment option in this therapeutic indication. The active ingredient was only recently approved (marketing authorisation on 19.04.2024). Based on the generally accepted state of medical knowledge, danicopan is not determined to be an appropriate comparator therapy for the present resolution.

In summary, the proximal complement inhibitors pegcetacoplan, danicopan and iptacopan were not determined to be an appropriate comparator therapy for crovalimab for the present resolution.

b) <u>Adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH) who have been receiving a C5 inhibitor for ≥ 6 months and are clinically stable</u>

With regard to patients who are clinically stable under treatment with a C5 inhibitor, the scientific-medical societies state that the therapy standard in terms of maintaining a clinically stable condition is treatment with a C5 complement inhibitor (eculizumab or ravulizumab) in analogy to the treatment of symptomatic patients with PNH and high disease activity. If the course of treatment with a C5 complement inhibitor is stable, treatment is continued in the long term.

In the overall assessment, the G-BA determines eculizumab or ravulizumab as equally appropriate comparator therapies for adult and paediatric patients 12 years of age or older with a body weight of 40 kg and above with haemolysis with clinical symptom(s) indicative of high disease activity (patient group a) as well as for those who are clinically stable after having been treated with eculizumab for at least the past 6 months (patient group b).

According to the written statement of the scientific-medical societies, optimal supportive treatment is an integral part of PNH therapy for both patient groups in addition to C5 inhibition.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

Courtesy translation – only the German version is legally binding.

2.1.3 Extent and probability of the additional benefit

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

a) Adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH) and haemolysis with clinical symptom(s) indicative of high disease activity

An additional benefit is not proven.

Justification:

For the proof of additional benefit in patient group a), the pharmaceutical company presented the results of the open-label, randomised, controlled, non-inferiority COMMODORE 2 study comparing crovalimab with eculizumab.

Patients with PNH who had never been treated with a complement inhibitor and who had at least one PNH-associated symptom and a lactate dehydrogenase (LDH) value ≥ 2 times the upper limit of normal (ULN) range within 3 months prior to screening were enrolled in the COMMODORE 2 study.

However, this therapeutic indication also includes patients who exhibit high disease activity despite pretreatment. No data are available from the COMMODORE 2 study for this treatment setting.

Adult patients were randomly allocated in a 2:1 ratio to treatment with crovalimab (N = 135) or eculizumab (N = 69). The duration of the randomised study phase was 24 weeks. The study also included a non-randomised study arm in which patients < 18 years of age were enrolled and treated with crovalimab (N = 6). Therefore, no relevant comparator data for the benefit assessment are available for paediatric patients.

In both study arms of the COMMODORE 2 study, the patients enrolled received a comparable level of supportive treatment in accordance with local care standards.

The co-primary endpoints of the COMMODORE 2 study were transfusion avoidance and haemolysis control. Endpoints on morbidity and adverse events (AEs) were collected as secondary endpoints.

The COMMODORE 2 study, which has been ongoing since October 2020, was conducted in 67 study sites in South America, Asia and Europe. The pre-specified primary data cut-off from 16.11.2022 was used for the benefit assessment.

Courtesy translation – only the German version is legally binding.

Extent and probability of the additional benefit

Mortality

Overall survival was not collected as a separate endpoint in the COMMODORE 2 study. The results on the endpoint of overall survival are based on the data on fatal AEs. There were no signs of statistically significant differences between the treatment groups.

Morbidity

Transfusion independence

The endpoint of transfusion independence in the COMMODORE 2 study was defined as the percentage of patients who did not receive a transfusion with red blood cell concentrate from the start of the study until week 25 and who did not require a transfusion according to the guidelines specified in the protocol. A transfusion with red blood cell concentrate was administered at

- a Hb value ≤ 9 g/dl with symptoms or signs of sufficient severity to justify a transfusion at the principal investigator's discretion,
- a 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.

A period of transfusion independence from the start of the study to week 25 is regarded as a long-term avoidance of transfusions in this therapeutic indication and is a patient-relevant endpoint. For the endpoint of transfusion independence, there was no statistically significant difference between the treatment groups.

Major Adverse Vascular Event (MAVE)

In the COMMODORE 2 study, major adverse vascular events were defined as the following events: Thrombophlebitis/ deep vein thrombosis, pulmonary embolism, myocardial infarction, transient ischaemic attack (TIA), unstable angina pectoris, renal vein thrombosis, acute peripheral vascular occlusion, mesenteric/ visceral venous thrombosis or infarction, mesenteric/ visceral arterial thrombosis or infarction, hepatic vein/ portal vein thrombosis (Budd-Chiari syndrome), cerebral arterial occlusion/ stroke, cerebral venous occlusion, renal artery thrombosis, gangrene (non-traumatic, non-diabetic), amputation (non-traumatic, non-diabetic), dermal thrombosis and other.

For the MAVE endpoint, there was no statistically significant difference between the treatment groups.

Courtesy translation – only the German version is legally binding.

Breakthrough haemolysis

The endpoint of breakthrough haemolysis was defined in the COMMODORE 2 study as the occurrence of at least one new or deterioration symptom or sign of intravascular haemolysis, such as fatigue, haemoglobinuria, abdominal pain, dyspnoea, anaemia (defined as haemoglobin < 10 g/dl), MAVE, dysphagia or erectile dysfunction, with the simultaneous presence of an elevated LDH value ≥ 2 x ULN (after a previous decrease to ≤ 1.5 x ULN due to treatment).

The endpoint of breakthrough haemolysis can be a patient-relevant endpoint in the present therapeutic indication in a suitable operationalisation, which should include the occurrence of noticeable symptoms of haemolysis in addition to an increase in the LDH value.

However, in the operationalisation presented, the occurrence of anaemia, defined as a haemoglobin value below 10 g/dl, with a simultaneous increase in the LDH value is also considered as an event in the endpoint of breakthrough haemolysis. Asymptomatic findings based solely on laboratory parameters (haemoglobin and LDH levels) are not considered directly patient-relevant. The endpoint of breakthrough haemolysis is therefore not considered patient-relevant in the operationalisation presented, which is why the available data are assessed as being unsuitable for deriving statements on patient-relevant effects.

Fatigue (FACIT-Fatigue)

The fatigue endpoint was collected using the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue. In the presented responder analyses on clinically relevant improvement, there was no statistically significant difference between the treatment groups.

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

The health status of the patients was assessed in the COMMODORE 2 study using the visual analogue scale (VAS) of the EQ-5D questionnaire. In the presented responder analysis on clinically relevant improvement, there was no statistically significant difference between the treatment arms.

Symptomatology (EORTC Item List 40; Patient Global Impression of Severity Survey)

Symptomatology was assessed in the COMMODORE 2 study using the EORTC Item List 40 (EORTC IL40) and the Patient Global Impression of Severity Survey (PGIS).

The EORTC IL40 is an item list with 6 scales for the symptoms of dysphagia, chest pain, abdominal pain, dyspnoea, headache and erectile dysfunction. The isolated use of an item list without collecting the core questionnaire is inappropriate. The item list EORTC IL40 is therefore not used for the present assessment.

The PGIS is a scale consisting of one item that patients use to assess the manifestation of PNH-associated symptomatology. In the COMMODORE 2 study, the PGIS was only collected at the start of the study and then again at week 33. At this time, the randomised study phase had already been completed for 8 weeks and the patients from the comparator arm had since been treated with crovalimab. The results of the PGIS are therefore not used for the present assessment.

Courtesy translation – only the German version is legally binding.

Quality of life

EORTC QLQ-C30

Quality of life was assessed in the COMMODORE 2 study using the scales of physical functioning, role functioning and global health status/ quality of life from the EORTC QLQ-C30 questionnaire. Further scales, such as the remaining functional scales of emotional functioning, cognitive functioning and social functioning as well as the symptom scales were not assessed.

According to the manual, the EORTC questionnaires are generally validated in full with all scales and must therefore be collected and presented in full. The presented scales therefore do not fully reflect the health-related quality of life and are unsuitable for the assessment of the additional benefit of crovalimab.

Quality of Life Questionnaire – Aplastic Anaemia/Paroxysmal Nocturnal Haemoglobinuria (QLQ-AA/PNH)

In the COMMODORE 2 study, the QLQ-AA/PNH questionnaire was only collected at the start of the study and then again at week 33. At this time, the randomised study phase had already been completed for 8 weeks and the patients from the comparator arm had since been treated with crovalimab. The results of the QLQ-AA/PNH are therefore unsuitable for the benefit assessment of crovalimab.

Side effects

Adverse events (AEs) in total

AEs occurred in about 77.8% of patients in the intervention arm and about 79.7% of patients in the control arm. 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.

Overall assessment

The results of the open-label, randomised controlled trial COMMODORE 2 comparing crovalimab versus eculizumab are available for the assessment of the additional benefit of crovalimab for the treatment of adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with PNH with haemolysis with clinical symptom(s) indicative of high disease activity.

Suitable data on the endpoints in the categories of mortality, morbidity and side effects are available for the benefit assessment. No suitable data were submitted for the assessment of health-related quality of life.

With regard to the patient-relevant endpoints in the categories of mortality, morbidity and side effects, there were neither advantages nor disadvantages of crovalimab compared to eculizumab.

In the overall assessment, there are therefore neither positive nor negative effects of crovalimab in comparison with eculizumab, so that an additional benefit of crovalimab for the treatment of adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with PNH with haemolysis with clinical symptom(s) indicative of high disease activity is not proven.

Courtesy translation – only the German version is legally binding.

b) Adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH) who have been receiving a C5 inhibitor for ≥ 6 months and are clinically stable

An additional benefit is not proven.

Justification:

For the proof of additional benefit in patient group b), the pharmaceutical company presented the results of the open-label, randomised COMMODORE 1 study. The original aim of the COMMODORE 1 study was to demonstrate the non-inferiority of crovalimab to eculizumab in patients with PNH who had previously received eculizumab for at least 6 months and had clinically stable disease at the start of the study. Stable disease was defined by an LDH value that did not exceed the upper limit of normal by more than 1.5 times at the start of the study and no MAVE in the 6 months prior to enrolment in the study.

Due to slow recruitment of study participants, randomisation was terminated prematurely before the planned approx. 200 patients were enrolled. Only approx. 45% of the recruitment target was achieved and the primary evaluation took place in parallel with the COMMODORE 2 study on 16.11.2022.

Adult patients were randomly assigned in a 1:1 ratio to a change of therapy to crovalimab (N = 45) or continuation of the existing therapy with eculizumab (N = 44) at the time of enrolment in the study. The duration of the randomised study phase was 24 weeks. In addition, the COMMODORE 1 study included a non-randomised study arm in which, among others, a child < 18 years of age with previous eculizumab therapy was enrolled and treated with crovalimab. Therefore, no relevant comparator data for the benefit assessment are available for paediatric patients.

Originally, the LDH value at week 25 was planned as the primary endpoint of the COMMODORE 1 study. After the premature termination of recruitment, the primary endpoint was changed to AE. Secondary endpoints in the categories of morbidity and quality of life were also collected.

The COMMODORE 1 study, which has been ongoing since September 2020, was conducted in 70 study sites in America, Asia and Europe.

The evaluations required by the Food and Drug Administration (FDA) were submitted in the dossier on 31.05.2023 as not all patients had completed the randomised study phase at the time of the early data cut-off from 16.11.2022, according to the information provided by the pharmaceutical company.

As part of the written statement procedure, the pharmaceutical company submitted a completely new evaluation of the COMMODORE 1 study. They justified this with a programming error that resulted in access to an incorrect data record, which would have potentially affected all analyses of the COMMODORE 1 study that were made specifically for the benefit assessment.

The corrected evaluations of the COMMODORE 1 study subsequently submitted as part of the written statement procedure were used for the benefit assessment.

Courtesy translation – only the German version is legally binding.

Extent and probability of the additional benefit

It should be noted that the respective operationalisations of the endpoints in the COMMODORE 1 study were carried out analogously to the collection of the respective endpoints in the COMMODORE 2 study. The explanations of the individual endpoints therefore apply to the COMMODORE 1 study as described above.

Mortality

In the COMMODORE 1 study, no deaths occurred during the 24-week primary treatment phase. The available data therefore do not show any relevant difference between the treatment arms.

Morbidity

Transfusion independence

In the COMMODORE 1 study, there was no statistically significant difference between the treatment groups in terms of transfusion independence.

Major Adverse Vascular Event (MAVE)

For the MAVE endpoint, there was no statistically significant difference between the treatment groups of the COMMODORE 1 study.

Breakthrough haemolysis

The endpoint of breakthrough haemolysis is not considered patient-relevant in the operationalisation presented for the reasons mentioned above, which is why the available data are assessed as being unsuitable for deriving statements on patient-relevant effects.

Fatigue (FACIT-Fatigue)

The endpoint of fatigue was collected in the COMMODORE 1 study using the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue. A statistically significant advantage of crovalimab over eculizumab was observed.

General health status (EQ-5D VAS)

The health status of the patients was assessed in the COMMODORE 1 study using EQ-5D VAS. In the presented responder analysis on clinically relevant improvement, there was no statistically significant difference between the treatment arms.

Symptomatology (EORTC IL40)

Symptomatology was assessed in the COMMODORE 1 study using the item list EORTC IL40. The item list EORTC IL40 is not used for the assessment of the additional benefit of crovalimab for the reasons stated above.

Courtesy translation – only the German version is legally binding.

Quality of life

EORTC QLQ-C30

Quality of life was assessed in the COMMODORE 1 study using the scales of physical functioning, role functioning and global health status/ quality of life from the EORTC QLQ-C30 questionnaire. For the reasons stated above, the data presented are unsuitable for the assessment of the additional benefit of crovalimab.

Side effects

Adverse events (AEs) in total

AEs occurred in about 79.5% of patients in the intervention arm and about 66.7% of patients in the control arm. The results were only presented additionally.

Serious AEs (SAEs)

For the endpoint of SAEs, no statistically significant difference was detected between the treatment groups.

Severe AEs

For the endpoint of severe AEs, there was a statistically significant difference to the disadvantage of crovalimab.

Therapy discontinuation due to AEs

In the COMMODORE 1 study, there was no therapy discontinuation due to AEs.

Overall assessment

The results of the open-label, randomised controlled trial COMMODORE 1 comparing crovalimab versus eculizumab are available for the assessment of the additional benefit of crovalimab for the treatment of adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH) who are clinically stable after having been treated with a C5 inhibitor for at least the past 6 months.

Suitable data on the endpoints in the categories of mortality, morbidity and side effects are available for the benefit assessment.

No deaths occurred in the COMMODORE 1 study, so that no difference was observed between the treatment groups with regard to the endpoint of mortality.

With regard to the endpoint category of morbidity, crovalimab showed an advantage over eculizumab for the fatigue endpoint, collected using FACIT-Fatigue. The risk of bias of the patient-reported endpoints is assessed as high due to the open-label study design.

There were no statistically significant differences between the treatment groups for the other patient-relevant endpoints in the morbidity category (transfusion independence, MAVE and general health status, collected using EQ-5D VAS).

No suitable data were submitted for the assessment of health-related quality of life.

With regard to side effects, crovalimab shows a disadvantage compared to eculizumab in the endpoint of severe AEs.

Courtesy translation – only the German version is legally binding.

In the overall analysis, an advantage of crovalimab in the fatigue endpoint is offset by a disadvantage in the endpoint of severe AEs.

In a weighted decision, the G-BA stated that an additional benefit of crovalimab over eculizumab for the treatment of adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria who are clinically stable after having been treated with a C5 inhibitor for at least the past 6 months is not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Piasky with the active ingredient crovalimab.

Crovalimab has been approved for the following therapeutic indication:

"Piasky as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH):

- In patients with haemolysis with clinical symptom(s) indicative of high disease activity.
- In patients who are clinically stable after having been treated with a complement component 5
  (C5) inhibitor for at least the past 6 months."

This results in the following patient groups:

a) Adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH) and haemolysis with clinical symptom(s) indicative of high disease activity

and

b) Adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH) who have been receiving a C5 inhibitor for ≥ 6 months and are clinically stable.

On patient group a)

The G-BA determined eculizumab or ravulizumab as the appropriate comparator therapy.

The results of the open-label, randomised, controlled COMMODORE 2 study comparing crovalimab with eculizumab are available. Results of the endpoints in the categories of mortality, morbidity and side effects were presented.

With regard to the patient-relevant endpoints in the categories of mortality, morbidity and side effects, there were neither advantages nor disadvantages of crovalimab compared to eculizumab. No suitable data were submitted for the assessment of health-related quality of life.

In the overall assessment, the additional benefit of crovalimab compared with eculizumab for the treatment of f adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH) with haemolysis with clinical symptom(s) indicative of high disease activity is not proven.

On patient group b)

The G-BA determined eculizumab or ravulizumab as the appropriate comparator therapy.

Courtesy translation – only the German version is legally binding.

The results of the open-label, randomised, controlled COMMODORE 1 study comparing crovalimab with eculizumab are available. Results of the endpoints in the categories of mortality, morbidity and side effects were presented.

With regard to mortality, no deaths occurred in the COMMODORE 1 study.

In the endpoint category of morbidity, there was an advantage with regard to the fatigue symptom. The risk of bias of the patient-reported endpoints is assessed as high due to the open-label study design.

For the other patient-relevant endpoints in the category of morbidity, there were no statistically significant differences between the treatment groups.

No suitable data were submitted for the assessment of health-related quality of life.

In terms of side effects, there was a disadvantage of crovalimab compared to eculizumab in severe adverse events.

A weighted decision of the overall assessment showed that the additional benefit of crovalimab over eculizumab for the treatment of adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH) who are clinically stable after having been treated with a C5 inhibitor for at least the past 6 months is not proven.

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

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

The resolution is based on the information from the resolutions on the benefit assessment of ravulizumab for the treatment of adults (resolution of 6 February 2020) and paediatric patients (resolution of 18 March 2022) with PNH.

The derivation of the patient numbers made by the pharmaceutical company in the dossier is for the most part mathematically comprehensible, but represents an underestimate, particularly due to the lack of consideration of patients with an outpatient diagnosis.

For this reason, the information on patients in patient populations a) and b) provided in the resolutions adopted in the comparable therapeutic indication is considered a better approximation of the SHI target population than the pharmaceutical company's estimate, despite existing uncertainties and deviating age and weight limits.

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 Piasky (active ingredient: crovalimab) at the following publicly accessible link (last access: 10 December 2024):

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

Courtesy translation – only the German version is legally binding.

Treatment with crovalimab 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 pass. The training material and the patient pass contain in particular information on serious infections, meningococcal infections and serious haemolysis post discontinuation of crovalimab. The patient pass also contains information about reactions in connection with an infusion and injection-related reactions.

There are no data on the switch-over to crovalimab in clinically unstable patients who continue to show high disease activity post treatment with a C5 inhibitor.

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: 15 February 2025).

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.

This resolution relates to the treatment of adult and paediatric patients 12 years of age or older with a weight of 40 kg and above. The doses of the medicinal product under assessment with the active ingredient crovalimab and the appropriate comparator therapy eculizumab or ravulizumab follow a body-weight-based dosage regimen.

The annual treatment costs shown refer to the first year of treatment.

a) Adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH) and haemolysis with clinical symptom(s) indicative of high disease activity

b) Adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH) who have been receiving a C5 inhibitor for ≥ 6 months and are clinically stable

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				
Crovalimab	≥ 40 kg to < 100 kg			
	Initial dosage regimen: Day 1	1.0	1	1.0

Courtesy translation – only the German version is legally binding.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	1 x weekly on day 2, 8, 15, 22 <u>Maintenance dosage regimen</u>: Continuously, 1 x every 28 days	4.0 12.0	1 1	4.0 12.0
	≥100 kg			
	<u>Initial dosage regimen:</u> Day 1 1 x weekly on day 2, 8, 15, 22 <u>Maintenance dosage regimen</u>: Continuously, 1 x every 28 days	1.0 4.0 12.0	1 1 1	1.0 4.0 12.0
Appropriate comparator therapy				
Patient populations a) and b)				
Ravulizumab	≥ 40 kg to < 60 kg			
	<u>Initial dosage regimen:</u> Once on day 1 <u>Maintenance dosage regimen</u>: Continuously, 1 x every 56 days	1.0 6.3	1 1	1.0 6.3
	≥ 60 kg to <100 kg			
	<u>Initial dosage regimen:</u> Once on day 1 <u>Maintenance dosage regimen</u>:	1.0	1	1.0

Courtesy translation – only the German version is legally binding.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	Continuously, 1 x every 56 days	6.3	1	6.3
	≥ 100 kg			
	Initial dosage regimen: Once on day 1 Maintenance dosage regimen: Continuously, 1 x every 56 days	1.0 6.3	1 1	1.0 6.3
Eculizumab	≥ 40 kg			
	Initial dosage regimen: 1 x every 7 days Maintenance dosage regimen: Continuously, every 12 to 16 days	4.0 21.6 – 28.5	1 1	4.0 21.6 – 28.5

Consumption:

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

Designation of the therapy	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					
Crovalimab	≥ 40 kg to < 100 kg				
	Initial dosage regimen				

Courtesy translation – only the German version is legally binding.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	Day 1: 1,000 mg[2] Day 2, 8, 15, 22: 340 mg Maintenance dosage regimen: 680 mg	1,000 mg 340 mg 680 mg	3 x 340 mg 340 mg 2 x 340 mg	1.0 4.0 12.0	3.0 x 340 mg 4.0 x 340 mg 24.0 x 340 mg
	≥100 kg				
	Initial dosage regimen Day 1[2]: 1,500 mg Day 2, 8, 15, 22: 340 mg Maintenance dosage regimen: 1,020 mg	1,500 mg 340 mg 1,020 mg	5 x 340 mg 340 mg 3 x 340 mg	1.0 4.0 12.0	5.0 x 340 mg 4.0 x 340 mg 36.0 x 340 mg
Appropriate comparator therapy					
Patient populations a) and b)					
Ravulizumab	≥ 40 kg to < 60 kg				
	Initial dosage regimen Day 1: 2,400 mg				

[2] According to PI, the 1st initial dose is administered as an intravenous infusion

Courtesy translation – only the German version is legally binding.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	<u>Maintenance dosage regimen</u>: 3,000 mg	2,400 mg 3,000 mg	8 x 300 mg 10 x 300 mg	1.0 6.3	8.0 x 300 mg 63.0 x 300 mg
	≥ 60 kg to <100 kg				
	<u>Initial dosage regimen Day 1:</u> 2,700 mg <u>Maintenance dosage regimen</u>: 3,300 mg	2,700 mg 3,300 mg	9 x 300 mg 3 x 1,100 mg	1.0 6.3	9.0 x 300 mg 18.9 x 1,100 mg
	≥ 100 kg				
	<u>Initial dosage regimen Day 1:</u> 3,000 mg <u>Maintenance dosage regimen</u>: 3,600 mg	3,000 mg 3,600 mg	10 x 300 mg 3 x 1,100 mg + 1 x 300 mg	1.0 6.3	10.0 x 300 mg 18.9 x 1,100 mg + 6.3 x 300 mg
Eculizumab	≥ 40 kg				
	<u>Initial dosage regimen:</u> 600 mg <u>Maintenance dosage regimen</u>: 900 mg	600 mg 900 mg	2 x 300 mg 3 x 300 mg	4.0 21.6 – 28.5	8.0 x 300 mg

Courtesy translation – only the German version is legally binding.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
					64.8 x 300 mg – 85.5 x 300 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 Sections 130 and 130 a 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					
Crovalimab 340 mg	1 IIS	€ 15,025.25	€ 1.77	€ 857.50	€ 14,165.75
Appropriate comparator therapy					
Eculizumab 300 mg	1 CII	€ 5,586.75	€ 1.77	€ 318.47	€ 5,266.28
Ravulizumab 300 mg	1 CIS	€ 4,655.73	€ 1.77	€ 265.29	€ 4,388.44
Ravulizumab 1,100 mg	1 CIS	€ 17,043.19	€ 1.77	€ 972.75	€ 16,068.44
Abbreviations: CIS = concentrate for the preparation of an infusion solution; IIS = concentrate for the preparation of an infusion solution; CII = concentrate for injection or infusion solution					

LAUER-TAXE® last revised: 15 February 2025

Costs for additionally required SHI services:

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

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

Courtesy translation – only the German version is legally binding.

Because there are no 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, no costs for additionally required SHI services need to be taken into account.

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

Courtesy translation – only the German version is legally binding.

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

Courtesy translation – only the German version is legally binding.

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

Courtesy translation – only the German version is legally binding.

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) Adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH) and haemolysis with clinical symptom(s) indicative of high disease activity

   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) Adult and paediatric patients 12 years of age or older with a weight of 40 kg and above with paroxysmal nocturnal haemoglobinuria (PNH) who have been receiving a C5 inhibitor for ≥ 6 months and are clinically stable

   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

At its session on 8 August 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 13 August 2024.

On 13 September 2024, the pharmaceutical company submitted a dossier for the benefit assessment of crovalimab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 13 September 2024 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products

Courtesy translation – only the German version is legally binding.

with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient crovalimab.

The dossier assessment by the IQWiG was submitted to the G-BA on 12 December 2024, and the written statement procedure was initiated with publication on the G-BA website on 16 December 2024. The deadline for submitting statements was 6 January 2025.

The oral hearing was held on 27 January 2025.

By letter dated 28 January 2025, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 14 February 2025.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 25 February 2025, and the proposed draft resolution was approved.

At its session on 6 March 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Courtesy translation – only the German version is legally binding.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	8 August 2023	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	13 August 2024	New determination of the appropriate comparator therapy
Working group Section 35a	14 January 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	27 January 2025	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	4 February 2025 18 February 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	25 February 2025	Concluding discussion of the draft resolution
Plenum	6 March 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 6 March 2025

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

Prof. Hecken

Courtesy translation – only the German version is legally binding.