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
Valoctocogene roxaparvovec (severe haemophilia A)

of 16 March 2023

Contents

1. Legal basis

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

For medicinal products approved for novel therapies within the meaning of Section 4, paragraph 9 Medicinal Products Act, there is an obligation to submit evidence in accordance with Section 35a, paragraph 1, sentence 3 SGB V. Medical treatment with such a medicinal product is not subject to the assessment of examination and treatment methods according to Sections 135, 137c or 137h.

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

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

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

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of

the medicinal product concerned has exceeded the turnover threshold according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published online 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 valoctocogene roxaparvovec on 15 September 2022 in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 15 September 2022.

Valoctocogene roxaparvovec for the treatment of severe haemophilia A (congenital factor VIII deficiency) in adult patients without a history of factor VIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5) is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999.

Valoctocogene roxaparvovec concerns a gene therapy within the meaning of Section 4, paragraph 9 Medicinal Products Act.

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

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 15 December 2022 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 G22-31) 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 assessed the studies relevant for the marketing authorisation considering 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 valoctocogene roxaparvovec.

[1] General Methods, version 6.1 from 24.01.2022. 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 valoctocogene roxaparvovec (Roctavian) according to the product information

ROCTAVIAN is indicated for the treatment of severe haemophilia A (congenital factor VIII deficiency) in adult patients without a history of factor VIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5).

Therapeutic indication of the resolution (resolution of 16 March 2023):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

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

Adults with severe haemophilia A (congenital factor VIII deficiency) without a history of factor VIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5)

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

Justification:
For the benefit assessment of valoctocogene roxaparvovec, the pharmaceutical company submits the single-arm intervention studies BMN 270-301 (GENEr8-1) and BMN 270-201 as well as a non-interventional observational study for external control (BMN 270-902).

The open-label, single-arm phase I/II dose escalation study BMN 270-201 investigated the safety, tolerability and efficacy of valoctocogene roxaparvovec in patients with severe haemophilia A. The population with doses compliant with the marketing authorisation is too small to provide relevant results for the benefit assessment (n = 7). Consequently, the BMN 270-201 study was not used for the benefit assessment.

The BMN 270-301 study is an open-label, single-arm, multicentre phase III study to assess the efficacy and safety of valoctocogene roxaparvovec in adults with severe haemophilia A. The study is divided into two cohorts. Patients from the observational study BMN 270-902 with an observation period of at least 6 months were enrolled (rollover population) as well as patients without prior participation in the observational study (direct enrolment). Adult men with haemophilia A and a residual factor VIII activity of 1 IU/dl or less according to medical history were enrolled. In addition, patients had to have received factor VIII prevention for at least 12 months prior to enrolment in the study and there had to be high-quality documentation of bleeding events and required factor VIII products during the preceding 12 months according to the pharmaceutical company. Patients with antibodies to AAV5 capsid, history of factor VIII antibodies and liver dysfunction were not enrolled. Patients received a single intravenous infusion of valoctocogene roxaparvovec. Factor VIII prevention should be discontinued approximately four weeks after the valoctocogene roxaparvovec infusion and from this point onwards should only be resumed as needed.

In addition, therapeutic administration of corticosteroids and/or immunosuppressive agents was possible with elevated ALT liver values. Approximately 79% of patients were treated with corticosteroids due to elevated ALT levels.

Efficacy and safety follow-up was conducted up to week 52 and further long-term follow-up up to 5 years after gene therapy administration. The primary endpoint of the BMN 270-301 study was the change in human factor VIII activity. In addition, the change in the annualised consumption of factor replacement therapy, the change in the annualised number of bleeding episodes requiring treatment were collected as secondary endpoints. In addition, patient-reported endpoints (including Haemo-QoL-A, EQ-5D-5L, Haemophilia Activities List) and adverse events were recorded. The pharmaceutical company has submitted a data cut-off of the still ongoing study dated 15 November 2021.

Before-after comparison

The pharmaceutical company submits an intra-individual before-after comparison as part of the benefit assessment. For this purpose, the pharmaceutical company compares, among other things, bleeding events under factor VIII prevention ("before", observational study BMN 270-902 or retrospectively collected data) with results after valoctocogene roxaparvovec infusion ("after", intervention study BMN 270-301).

The before-after comparison submitted has considerable methodological limitations.

There are unequal collection types between the previously collected data compared to the data collected in the intervention study BMN 270-301. Data on patients who were directly enrolled in the BMN 270-301 study were collected retrospectively. For the patients from the observational study BMN 270-902 (rollover population), a mixture of retrospectively and prospectively collected data is available. In addition to the prospective data from the observational study, data for further 6 months prior to enrolment in the observational study were collected retrospectively. Retrospectively collected data are not considered comparable to the prospective data from the intervention study.

Furthermore, it cannot be assessed whether the same conditions for the use of prevention/therapy exist before the intervention study compared to the observation period after the start of the study.

In addition, the prospective data from the observational study BMN 270-902 were not collected over a sufficiently long period of time of about one year, so that risk of bias due to extrapolations cannot be excluded when annualising the prospective data.

Overall, the before-after comparison is not considered sufficiently valid and cannot be used for the benefit assessment.

Indirect comparisons

The pharmaceutical company submits two further indirect comparisons with external controls. It compares bleeding events in the rollover population of the BMN 270-301 study with those patients who were not enrolled in the BMN 270-301 study from the observational study BMN 207-902. In addition, the pharmaceutical company compares the analysis population of the BMN 270-301 study with the baseline characteristics of HAVEN 3 group D (emicizumab study).

The two indirect comparisons are not used for the benefit assessment due to the absence of sufficient information to conduct a methodological assessment as part of the benefit assessment.

Mortality

There was one death in the BMN 270-301 study.

Morbidity

Bleeding events

Patients in the BMN 270-301 study document any bleeding events and use of factor VIII prevention in a personal patient diary. During the screening period, patients received training on how to keep the patient diary.

In addition to results on descriptive bleeding frequencies, annualised bleeding rates are presented for all bleeding events and differentiated according to joint bleeding, bleeding in the target joint, bleeding that is not joint bleeding, spontaneous bleeding, bleeding due to trauma and treated bleeding. Bleeding due to surgery or other intervention is not considered. The treatment must be exogenous factor VIII replacement therapy. Target joints are defined as problematic joints with any of the following symptoms: Chronic joint pain, chronic synovitis, haemophilic arthropathy, limitation of movement or recurrent bleeding.

The pharmaceutical company submitted results for the entire study period, i.e. from valoctocogene roxaparvovec infusion, as well as from the planned end of factor VIII prevention (all periods from week 5) or the actual end of factor VIII prevention ("post-prophylaxis"). In the resolution, the results on bleeding events are presented for the entire study period, as bleeding in the entire period after valoctocogene roxaparvovec administration is patient-relevant.

The bleeding events as well as the bleeding rate for "no bleeding" and "all bleeding events", respectively, are presented additionally, as no definition of a "suspected" bleeding event is given, so that there is ambiguity about the bleeding events or the "suspected" bleeding events.

Approximately 31% of patients had no bleeding after administration of valoctocogene roxaparvovec, 71% had no joint bleeding and 94% had no bleeding in the target joint. In 59% of the patients, no treated bleeding occurred during the entire course of the study. The estimated annual bleeding rate (ABR) for "all bleeding events" is 1.45 and for "treated bleeding events" 0.9.

Health status assessed by EQ-5D-5L VAS

The health status is assessed in the BMN 270-301 study using the EQ-5D-5L visual analogue scale (VAS). With the VAS, people rate their general health status on a scale from 0 to 100 in relation to the current day. A value of 0 corresponds to the worst perceivable health status and a value of 100 to the best perceivable health status.

The endpoint shows an increase in the values from baseline to week 104. As the available before-after comparison is not recognised, no statement on the extent of the additional benefit can be derived.

Haemophilia Activities List (HAL)

The HAL is a patient-reported questionnaire that measures the impact of haemophilia on functional abilities of adults. The first part of the HAL consists of 42 items that can be divided into seven domains, each asking about specific difficulties caused by haemophilia. The answers are given on a 6-point scale (1: impossible, 2: always - 6: never). The normalised sum scores have values between 0 (most severe impairments) and 100 (no impairments whatsoever). The HAL was used in the BMN 270-301 study.

The HAL results show a change from baseline to week 104, indicating less pronounced functional impairment. As the available before-after comparison is not recognised, no statement on the extent of the additional benefit can be derived.

Factor VIII activity (presented additionally)

The endpoint factor VIII activity is the primary endpoint of the BMN 270-301 study. Factor VIII activity was measured using a chromogenic coagulation assay. There is an increase in the mean value at week 104 compared to baseline.

Due to the known natural course of the disease, it cannot be assumed that patients suffering from severe haemophilia A will spontaneously acquire clinically relevant higher factor VIII activity in the natural course of their disease. The course of factor VIII activity in the long term beyond the observation period of the BMN 270-301 study remains unclear.

The endpoint factor VIII activity is a parameter that is not patient-relevant per se as it is a laboratory parameter. The results for the endpoint were presented in the resolution because it is the primary endpoint of the BMN 270-301 study and an important parameter for therapy management.

In addition to factor VIII activity, the BMN 270-301 study recorded concomitant therapy with factor VIII preparations. Factor VIII prevention should be discontinued approximately four weeks after the valoctocogene roxaparvovec infusion and from this point onwards should only be resumed as needed.

Only 4.5% (n = 6) of patients resumed prophylactic therapy with factor VIII preparations at least 5 weeks after valoctocogene roxaparvovec administration or started treatment with emicizumab. In 44% (n = 59) of patients, factor VIII treatment was given in the period from week 5 after valoctocogene roxaparvovec administration or from the time 3 days after the end of factor VIII prevention (whichever occurred last) until the last visit before the data cut-off. Factor VIII therapy could be resumed as needed and could include prophylactic factor VIII administration as well as treatments on demand for acute bleeding episodes. In the same period, 56% (n = 75) of the patients remained without any treatment with factor VIII preparations (neither as prevention nor as treatment on demand).

Long-term avoidance of regular prevention or treatments on demand with coagulation factor preparations may be patient-relevant, provided that other endpoints (e.g. bleeding rate) are not negatively affected as a result.

As the available before-after comparison is not recognised, no statement on the extent of the additional benefit can be derived. In addition, there are no data on whether these are long-term effects.

Quality of life

Haemophilia-specific Quality of Life Questionnaire for Adults (Haemo-QoL-A)

The Haemo-QoL-A is a patient-reported questionnaire to measure quality of life in adults with haemophilia and is used in the BMN 270-301 study. The questionnaire consists of 41 items, divided into six domains: physical functioning, role functioning, worry, consequences of bleeding, emotional impact, treatment concerns. The reference period is the last four weeks. Answers are given on a scale from 0 ("never") to 5 ("always") and can be transformed to a scale from 0 to 100. In addition to the total score, domain scores are formed. Higher values indicate a higher health-related quality of life or fewer impairments.

The total score shows an increase from baseline to week 104. The individual domain scores also show an increase from baseline to week 104. As the available before-after comparison is not recognised, no statement on the extent of the additional benefit can be derived.

Side effects

Adverse events occurred in all patients in the BMN 270-301 study. Adverse events of CTCAE grade ≥ 3 were documented in approx. 31% of patients. Serious adverse events were reported in approximately 18% of patients.

Overall assessment

Data from the single-arm study BMN 270-301 are available on the endpoints of mortality, morbidity, quality of life and side effects for valoctocogene roxaparvovec for the treatment of adults with severe haemophilia A (congenital factor VIII deficiency) without a history of factor VIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5).

In addition, a before-after comparison based on the observational study BMN 270-902 or retrospectively collected data and the intervention study BMN 270-301 was presented. The before-after comparison has considerable methodological limitations and is not considered sufficiently valid to be used for the benefit assessment.

Overall, there are no appropriate data for a comparative assessment. Thus, quantification of the extent of the additional benefit is not possible on the basis of the data presented.

No statements on the extent of additional benefit can be derived from the overall analysis of the available results. A quantitative assessment of the extent of the effect and a quantification of the additional benefit according to the categories "minor", "considerable" or "major" on the basis of the data presented is not possible. Taking into account the severity of the disease, the written statements and the oral hearing, the G-BA classifies the extent of additional benefit of valoctocogene roxaparvovec for the treatment of severe haemophilia A in adults as non-quantifiable on the basis of the criteria in Section 5, paragraph 7 of the AM-NutzenV since the scientific data does not allow quantification.

Significance of the evidence

Only single-arm data from the BMN 270-301 study could be considered for the benefit assessment. The risk of bias of the single-arm study data is estimated to be high at study and endpoint level. The significance of the evidence is classified as 'hint'.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Roctavian with the active ingredient valoctocogene roxaparvovec.

Roctavian was approved under "special conditions" as an orphan drug for the treatment of adults with severe haemophilia A (congenital factor VIII deficiency) without a history of factor VIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5).

Results from the single-arm study BMN 270-301 are available on the endpoints of mortality, morbidity, quality of life and side effects for valoctocogene roxaparvovec for the treatment of adults with severe haemophilia A (congenital factor VIII deficiency) without a history of factor VIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5).

In addition, a before-after comparison based on the observational study BMN 270-902 or retrospectively collected data and the intervention study BMN 270-301 was presented. The present before-after comparison has considerable methodological limitations and is not considered sufficiently valid to be used for the benefit assessment.

Overall, there are no appropriate data for a comparative assessment. Thus, quantification of the extent of the additional benefit is not possible on the basis of the data presented.

In the overall assessment, a hint for a non-quantifiable additional benefit is identified since the scientific data basis does not allow quantification.

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

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

The G-BA takes into account the patient figures subsequently submitted in the written statement of the pharmaceutical company.

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 Roctavian (active ingredient: valoctocogene roxaparvovec) at the following publicly accessible link (last access: 3 February 2023):

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

By resolution of 16 June 2022, the necessity of a resolution pursuant to Section 136a , paragraph 5 SGB V in accordance with Chapter 9, Section 5, sentence 2 VerfO was established for the use of the ATMP valoctocogene roxaparvovec in the therapeutic indication "Treatment of haemophilia A". As soon as corresponding regulations on quality assurance measures according to the ATMP Quality Assurance Guideline come into force, they must also be observed.

Treatment with valoctocogene roxaparvovec should only be initiated and monitored by doctors experienced in treating haemophilia and/or bleeding disorders.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide information material for medical professionals and patients as well as a patient card. The information material as well as the patient card contain instructions especially regarding the increased risk of liver toxicity, horizontal transmission and germline transmission, development of factor VIII inhibitors, malignancy associated with integration of the vector genome, and thromboembolism under administration of valoctocogene roxaparvovec.

This medicinal product was approved under "special conditions". This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 March 2023).

Valoctocogene roxaparvovec is a gene therapy intended for administration as a single dose by single intravenous infusion.

The recommended dose is 6 x 10^{13} vector genomes per kilogram (vg/kg) of body weight. For dosages depending on body weight, the average body measurements of male patients from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight: 85.0 kg)[2], as haemophilia predominantly affects the male sex.

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				
Valoctocogene roxaparvovec	Single dose	1	1	1

Consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Valoctocogene roxaparvovec	6 x 10^{13} vg/kg BW	510 x 10^{13} vg	31.88 x 2 x 10^{13} x 8 ml	1	31.88 x 16 x 10^{13} vg

Costs:

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					
Valoctocogene roxaparvovec 2 x 10^{13} vg/ml	1 INF	€ 74,557.19	€ 2.00	€ 7,293.75	€ 67,261.44

LAUER-TAXE® last revised: 1 March 2023

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.

[2] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

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.

Prior to the use of valoctocogene roxaparvovec, AAV5 antibody testing should be performed using an correspondingly validated test. There is not yet a billing number for the test in the EBM catalogue. AAV tests in general are billed via code 32641 "Similar investigations with indication of antibody specificity".

Designation of the therapy	Designation of the service	Number	Unit cost	Costs per patient per year
Medicinal product to be assessed: Valoctocogene roxaparvovec				
Valoctocogene roxaparvovec	AAV5 antibody testing	1	incalculable	

2.5 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 valoctocogene roxaparvovec

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

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

3. Bureaucratic costs calculation

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

4. Process sequence

On 15 September 2022, the pharmaceutical company submitted a dossier for the benefit assessment of valoctocogene roxaparvovec to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 15 December 2022 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 written statements was 5 January 2023.

The oral hearing was held on 23 January 2023.

An amendment to the benefit assessment with a supplementary assessment was submitted on 7 February 2023.

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 7 March 2023, and the proposed resolution was approved.

At its session on 16 March 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	6 December 2022	Information of the benefit assessment of the G-BA
Working group Section 35a	18 January 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	23 January 2023	Conduct of the oral hearing
Working group Section 35a	1 February 2023; 15 February 2023; 1 March 2023	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	7 March 2023	Concluding discussion of the draft resolution
Plenum	16 March 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 March 2023

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

Prof. Hecken