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

Etranacogene dezaparvovec (haemophilia B)

of 19 October 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 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 etranacogene dezaparvovec on 1 May 2023 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 28 April 2023.

Etranacogene dezaparvovec for the treatment of severe and moderately severe haemophilia B (congenital Factor IX deficiency) in adults without a history of Factor IX inhibitors 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.

Etranacogene dezaparvovec 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 1 August 2023 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 made its resolution on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G12-01) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for the approval with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods 1 was not used in the benefit assessment of etranacogene dezaparvovec.

[1] General Methods, version 6.1 of 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 Etranacogene dezaparvovec (Hemgenix) according to the product information

Hemgenix is indicated for the treatment of severe and moderately severe Haemophilia B (congenital Factor IX deficiency) in adult patients without a history of Factor IX inhibitors.

Therapeutic indication of the resolution (resolution of 19 October 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 etranacogene dezaparvovec is assessed as follows:

For adults with severe and moderately severe haemophilia B (congenital Factor IX deficiency) without a history of Factor IX inhibitors, there is a hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Justification:

For the benefit assessment of etranacogene dezaparvovec, the pharmaceutical company submits both an intra-individual before-after comparison within the single-arm phase III study CT-AMT-061-02 (hereinafter HOPE-B) and an indirect comparison of the HOPE-B study and the PROLONG-9FP study as an external control.

In addition, the open-label, single-arm phase IIb study CT-AMT-061-01 is presented, which only includes three patients and is not used to derive an additional benefit due to the small number of patients.

The HOPE-B study is an open-label, single-arm, multicentre phase III study to evaluate the efficacy and safety of etranacogene dezaparvovec in adults with severe and moderately severe haemophilia B. The study enrolled 54 men aged 18 years and older and with Factor IX activity ≤ 2%, who had been receiving stable treatment with Factor IX prophylaxis for at least two months prior to screening, treated with etranacogene decaparvovec. Among other things, subjects with a history of Factor IX antibodies and functional impairments of the liver were not enrolled. Etranacogene dezaparvovec was administered by a single intravenous infusion. The primary endpoint of the study was the change in annualised bleeding rate (ABR). In addition, further endpoints in the category of morbidity, health-related quality of life and side effects were collected (see below). The total study duration of approximately 5.5 years is composed of a 26-week lead-in period, a 52-week treatment and post-treatment period, and a long-term follow-up period of 4 years. For the benefit assessment, the 2-year data cut-off with study report dated 20 June 2022 was submitted.

Before-after comparison

The pharmaceutical company submits an intra-individual before-after comparison as part of the benefit assessment. For this purpose, the annualised bleeding rate of the 2-year follow-up period after treatment is compared with the 6-month lead-in period in which continuous FIX prophylaxis was used.

The before-after comparison submitted has the following methodological limitations.

A major point of criticism relates to the duration of observation of the patients in the study periods. While two years of follow-up data are available to assess the treatment effects of the intervention, the lead-in period was only six months.

Furthermore, it cannot be assessed whether the same conditions for the use of prevention or therapy exist in the lead-in phase compared to the post treatment period. In addition, the prospective data from the lead-in phase of the HOPE-B study 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.

Further uncertainties result from an insufficient definition of the study medication in the lead-in period, so that this control intervention cannot be assessed, as well as from the differences between the study periods in the collection of bleeding events by means of an e-diary with e.g. reminder function or as a paper diary.

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

Indirect comparison

The pharmaceutical company also submits an indirect comparison of etranacogene dezaparvovec (HOPE-B study) with albutrepenonacog (PROLONG-9FP study) as an external control, which was conducted as part of a technical report on indirect comparisons of etranacogene decaparvovec with four recombinant Factor IX preparations.

The indirect comparison is not used for the benefit assessment due to limitations caused by the selected analysis population of the HOPE-B study as well as criticisms regarding the identification of confounders, including the lack of a systematic search for relevant factors and the structural equality between the compared study populations.

Mortality

One death occurred in the HOPE-B study.

Morbidity

Bleeding events and annualised bleeding rates (ABR)

The endpoint of ABR is the primary endpoint of the HOPE-B study. In addition, any bleeding events were collected in an electronic diary (e-diary). During the lead-in period, patients received training on how to keep the patient diary.

In addition to results on the number of bleeding events, annualised bleeding rates are presented for all bleeding events and differentiated by bleeding type (joint bleeding, spontaneous bleeding, bleeding due to trauma) for all bleeding events and for bleeding events treated with Factor IX. In particular, bleeding that requires treatment is considered patient-relevant.

In addition to the results on ABR for the observation period of 7 to 24 months from the dossier, the pharmaceutical company submitted results for the entire study period of 0 to 24 months within the framework of the written statement procedure. In the resolution, the results on bleeding events are presented for the entire study period, as bleeding in the entire period after etranacogene dezaparvovec administration is patient-relevant.

Approximately 43% of patients did not experience any bleeding between day 22 and month 24 after receiving etranacogene dezaparvovec. In addition, about 61% of the patients did not experience any Factor IX-treated bleeding during the entire course of the study.

The estimated annual bleeding rate (ABR) for "all bleeding events" is 1.01 and for "bleeding events treated with Factor IX" 0.82.

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

The health status is assessed in the HOPE-B study using the EQ-5D-5L visual analogue scale (VAS). With the VAS, subjects 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 month 24. As the available before-after comparison is not recognised, no statement on the extent of the additional benefit can be derived.

Functional impairment using 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 results show a change from baseline to month 24, 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.

Pain using Brief Pain Inventory – Short Form (BPI-SF)

The BPI-SF questionnaire comprises 15 items. 11 items are assigned to the domains of pain severity (4 items) and pain interference (7 items). The items are answered on a scale from 0 (no pain or no impairment) to 10 (worst pain imaginable or most severe interference). The reference period is the last 24 hours. The remaining 4 items of the questionnaire measure the presence and location of pain as well as the use and efficacy of pain medication.

In the HOPE-B study, the patient-reported BPI-SF was used to assess the severity of pain and the extent to which it interferes with daily life.

The BPI-SF results show a change from baseline to month 24, indicating less pronounced interference due to pain. As the available before-after comparison is not recognised, no statement on the extent of the additional benefit can be derived.

Factor IX activity

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

The endpoint factor IX activity is a parameter that is not patient-relevant per se as it is a laboratory parameter. The results for the endpoint were only presented additionally in the resolution.

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 Index for Adults (Ham-A-QoL)

The Ham-A-QoL is a patient-reported questionnaire to measure quality of life in adults with haemophilia and is used in the HOPE-B 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.

Depending on the domain, mean changes between 1 and 10 points were reported from baseline to month 24, with a range of mean baseline values of 10 - 44 points. Due to the uncontrolled design, no conclusions can be drawn regarding the effects of etranacogene dezaparvovec on quality of life.

Side effects

Within the framework of the evaluations of the safety endpoints, no additional evaluations are available that do not take disease-related events or events of the underlying disease into account. Therefore, it cannot be excluded that events of the underlying disease are included in the observed adverse events (AEs).

Adverse events occurred in all patients of the HOPE-B study. Until the 2-year data cut-off, severe AEs had occurred in 20% of the 54 patients and serious AEs in 26%. In one patient, an AE led to premature discontinuation of the infusion, so that only a partial dose was administered.

Overall assessment

Data from the single-arm CT-AMT-061-02 (HOPE-B) study on mortality, morbidity, quality of life and side effects are available for etranacogene dezaparvovec for the treatment of adults with severe and moderately severe haemophilia B (congenital Factor IX deficiency) without a history of Factor IX inhibitors.

In addition, a before-after comparison based on the HOPE-B study and an indirect comparison of etranacogene dezaparvovec in the HOPE-B study and albutrepenonacog (PROLONG-9FP study) were presented. Both of these comparisons have considerable methodological limitations and are 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 etranacogene dezaparvovec for the treatment of severe and moderately severe haemophilia B 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 HOPE-B 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 Hemgenix with the active ingredient etranacogene dezaparvovec.

Hemgenix received a conditional marketing authorisation as an orphan drug for the treatment of severe and moderately severe Haemophilia B (congenital Factor IX deficiency) in adult patients without a history of Factor IX inhibitors.

Results from the single-arm CT-AMT-061-02 (HOPE-B) study on mortality, morbidity, quality of life and side effects are available for etranacogene dezaparvovec for the treatment of adults with severe and moderately severe haemophilia B (congenital Factor IX deficiency) without a history of Factor IX inhibitors.

In addition, a before-after comparison based on the HOPE-B study and an indirect comparison of etranacogene dezaparvovec in the HOPE-B study and albutrepenonacog (PROLONG-9FP study) were presented. Both of these comparisons have considerable methodological limitations and are not considered sufficiently valid to be used for the benefit assessment.

Overall, due to the single-arm study results, there are no suitable data for an assessment that would allow quantification of the extent of additional benefit. 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 resolution is based on the information and the basic approach from the dossier of the pharmaceutical company. This information is based on figures from the German Haemophilia Registry (DHR) and is subject to uncertainties.

These uncertainties result from the fact that only patients with severe haemophilia were included for the lower limit of the patient numbers and that the percentage value for patients with Factor IX inhibitors was only applied to the upper limit of the patient numbers. In addition, the exclusion of patients who have no documented effect for etranacogene decaparvovec due to the AAV5 antibody titre is considered inappropriate.

Against the background of the uncertainty of individual steps of the pharmaceutical company, the calculation of patient numbers is adjusted as follows: Subjects with moderate and severe haemophilia B, i.e. only the pharmaceutical company's submitted upper limit, are used. In addition, the percentage value for Factor IX inhibitors is applied to this information as well as no limitation regarding proven efficacy is applied.

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 Hemgenix (active ingredient: etranacogene dezaparvovec) at the following publicly accessible link (last access: 4 July 2023):

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

By resolution of 1 June 2023, 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 etranacogene dezaparvovec in the therapeutic indication "Treatment of haemophilia B". By resolution of 25 July 2023, it was decided to initiate a written statement procedure on the amendment of the ATMP-QS-RL on the initial version of Annex IV - Gene therapeutics for haemophilia. 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 etranacogene dezaparvovec 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 training material that contains information for medical professionals and patients (incl. patient card). The training material contains in particular information and warnings regarding the increased risk of liver toxicity, horizontal transmission and germline transmission, development of factor IX inhibitors, malignancy associated with vector genome integration, and thromboembolism under etranacogene dezaparvovec.

This medicinal product received a conditional marketing authorisation. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency 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 requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 1 October 2023).

Etranacogene dezaparvovec is a gene therapy intended for administration as a single dose by single intravenous infusion.

The recommended dose is 2 x 10^{13} genome copies per kilogram (gc/kg) of body weight, which corresponds to 2 ml/kg 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				
Etranacogene dezaparvovec	Single dose	1	1	1

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

Consumption:

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					
Etranacogene dezaparvovec	2 ml/kg BW (= 2 x 10^{13} gc/kg BW)	170 ml (= 170 x 10^{13} gc)	17 x 10 ml	1	17 x 10 ml

Costs:

Costs of the medicinal products:

According to Chapter 5 Section 9, paragraph 7, sentences 1 and 3 VerfO, the pharmaceutical company shall report the costs for the statutory health insurance measured against the pharmacy sales price and the costs actually incurred by the health insurance funds; if a presentation of the costs measured against the pharmacy sales price is not possible, the costs shall be presented on the basis of other suitable data. The direct costs of the statutory health insurance over a certain period of time are decisive.

A pharmacy sales price is not available for etranacogene dezaparvovec. There is no price information in the LAUER-TAXE® as of 1 October 2023 or other publicly available information regarding the costs currently incurred for etranacogene dezaparvovec in the statutory health insurance.

Both in the context of the dossier and in the written statement procedure carried out, the pharmaceutical company did not submit any suitable information regarding the direct costs of the therapy of etranacogene dezaparvovec for the patients in the statutory health insurance. A one-off price was neither publicly announced nor communicated to the G-BA.

Against this background, the direct costs of treatment with the medicinal product Hemgenix with the active ingredient etranacogene dezaparvovec cannot be presented.

Costs for additionally required SHI services:

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

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

.No additionally required SHI services are taken into account for the cost representation.

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

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

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is authorised exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or

- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

In the case of information on "determined" or "undetermined" combinations, the assessed medicinal product can be used in a combination therapy according to this information on the basis of the marketing authorisation under Medicinal Products Act. For the designation, the G-BA, within the scope of its legislative discretion, uses the constellation of a "determined" or an "undetermined" combination as a justifiable interpretation variant.

If a designation as a so-called determined or as a so-called undetermined combination is omitted due to the lack of information on a combination therapy in the product information of the assessed medicinal product, the non-designation in the resolution according to Section 35a, paragraph 3, sentence 1 SGB V does not affect the possibility that the assessed medicinal product can be used in an open-label combination under marketing authorisation regulations.

Concomitant active ingredient:

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1

SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Adults with severe and moderately severe Haemophilia B (congenital Factor IX deficiency) without a history of Factor IX inhibitors

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

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 28 April 2023, the pharmaceutical company submitted a dossier for the benefit assessment of etranacogene dezaparvovec to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 1 August 2023 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting statements was 22 August 2023.

The oral hearing was held on 11 September 2023.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the written statement procedure was submitted on 27 September 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 10 October 2023, and the proposed resolution was approved.

At its session on 19 October 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	25 July 2023	Information of the benefit assessment of the G-BA
Working group Section 35a	5 September 2023	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	11 September 2023	Conduct of the oral hearing
Working group Section 35a	20 September 2023 4 October 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	10 October 2023	Concluding discussion of the draft resolution
Plenum	19 October 2023	Adoption of the resolution on the amendment of the AM-RL

Berlin, 19 October 2023

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

Prof. Hecken