Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Etranacogene dezaparvovec (haemophilia B); requirement of routine practice data collection and evaluations – Revision

From 2 July 2026

Contents

1. Legal basis

According to Section 35a, paragraph 3b, sentence 1 SGB V, the Federal Joint Committee (G-BA) can demand the pharmaceutical company to submit routine practice data collections and evaluations for the purpose of the benefit assessment within a reasonable period of time for the following medicinal products:

1. in the case of medicinal products authorised to be placed on the market in accordance with the procedure laid down in Article 14, paragraph 8 of Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136 from 30.04.2004, p. 1), as last amended by Regulation 162 Rules of Procedure last revised: 16 December 2020 (EU) 2019/5 (OJ L 4 from 07.01.2019, p. 24), or for which a marketing authorisation has been granted in accordance with Article 14-a of Regulation (EC) No. 726/2004; and
2. for medicinal products approved for the treatment of rare diseases under Regulation No. 141/2000.

According to Section 35a, paragraph 3b, sentence 10 SGB V in conjunction with Chapter 5, Section 60 Rules of Procedure of the G-BA (VerfO), the G-BA review the data obtained and the obligation to collect data at regular intervals, at least every eighteen months.

2. Key points of the resolution

At their session on 12 May 2023, the G-BA decided on the requirement of routine practice data collection and evaluations for the active ingredient etranacogene dezaparvovec in accordance with Section 35a SGB V.
In accordance with the information in the resolution of 12 May 2023, a first interim analysis must be carried out after 18 months in accordance with the specifications in the study protocol and statistical analysis plan, and submitted to the G-BA. In the process, a check for discontinuation due to futility must also be carried out for each interim analysis. Based on this interim analysis, a final sample size estimate will also be made using the more precise effect assumptions rendered possible. Review of data collection resulted in changes to the G-BA's requirements for routine practice data collection and evaluations.
Subsequent to the publication of the resolution on the G-BA website, there has been further development with regard to the generally recognised state of medical knowledge, taking into account the resolutions on the benefit assessment of marstacimab from 17 July 2025 and of concizumab from 19 March 2026.

On the changes in detail

As part of the 1st interim analysis presented, the pharmaceutical company did not carry out a futility check and an updated sample size estimate. As justification, the pharmaceutical company stated that the current number of patients recruited is insufficient to make a reliable, updated sample size estimate. The pharmaceutical company cited several reasons for the delay in recruitment, such as the clarification of the reimbursement of etranacogene

dezaparvovec only eight months after the start of the routine practice data collection, as well as the protracted processes involved in the certification of study sites. However, the information provided by the pharmaceutical company indicated a positive trend in recruitment, and it is expected that this increase will continue steadily. In order to speed up recruitment, the pharmaceutical company have taken further measures, including, for example, closer communication with the study sites. In addition to the small sample size, the individual durations of observation are currently too short to allow for reliable estimates of the primary endpoint of haemorrhage (annualized bleeding rate). Due to the absence of an updated sample size estimate, the pharmaceutical company did not carry out a futility check. The pharmaceutical company therefore wants to extend the recruitment and observation period and requests a corresponding adjustment to the deadline for submitting analyses of the data collected as part of the routine practice data collection.

The reasons given by the pharmaceutical company for the absence of an updated sample size estimate and the missing futility check are understandable. The request by the pharmaceutical company to continue recruitment is also understandable given the circumstances.

The final sample size estimate should therefore be submitted at the 2nd interim analysis. The 2nd interim analysis will also be postponed by 8 months; instead of 36 months, it shall take place 44 months after the start of the routine practice data collection in order to ensure submission of sufficiently significant data. The previously required 3rd interim analysis is therefore cancelled, as a further interim analysis just a few months before the date of the renewed benefit assessment is considered purposeless. In addition, the information regarding the timing of the interim analyses to be submitted has been clarified: interim analyses shall be submitted 18 and 44 months after the start date of routine practice data collection to be defined by means of a declaratory resolution.

Further development with regard to the generally recognised state of medical knowledge, taking into account the resolutions on the benefit assessment of marstacimab from 17 July 2025 and of concizumab from 19 March 2026:

By resolution of 17 July 2025 on the benefit assessment of marstacimab, the G-BA was unable to identify any additional benefit of marstacimab over the appropriate comparator therapy for adults and adolescents 12 years of age and older with severe haemophilia B (congenital Factor IX deficiency, FIX < 1%) without Factor IX inhibitors for routine prophylaxis. The label-enabling, open-label, single-arm phase III BASIS study with an intra-individual before-and-after comparison was submitted for the benefit assessment; this study was deemed unsuitable for the assessment of an additional benefit as it lacked a comparison with the appropriate comparator therapy.

Similarly, by resolution of 19 March 2026 on the benefit assessment of concizumab, the G-BA was unable to identify any additional benefit thereof for adults and adolescents 12 years of age and older with severe and moderate haemophilia B (FIX ≤ 2%) without Factor IX inhibitors, for whom routine prophylaxis is indicated, compared with the appropriate comparator therapy. The label-enabling, partly randomised, open-label Explorer8 study with a comparison between routine prophylaxis with concizumab and treatment on demand with Factor products was submitted for the benefit assessment; this study was deemed unsuitable for the assessment of an additional benefit as it lacked a comparison with the appropriate comparator therapy.

In the written statement procedure for the active ingredients marstacimab and concizumab, the Society for Thrombosis and Haemostasis Research (GTH), together with the German Society for Haematology and Medical Oncology (DGHO), stated that the antibodies marstacimab and concizumab are based on a new pathophysiological concept: the inhibition of the Tissue Factor Pathway Inhibitor (TFPI) in order to normalise thrombin formation. This cannot be achieved with the current replacement therapy using Factor products, meaning that TFPI inhibitors would represent an important add-on to the treatment of haemophilia B.

Taking into account the above aspects, the G-BA consider marstacimab and concizumab to be a relevant additional comparator for the requirement of routine practice data collection for etranacogene dezaparvovec, which is why the amendment to the Pharmaceuticals Directive on which the present resolution is based is considered appropriate and necessary. On the basis of current evidence and taking into account the current German healthcare context, the G-BA determined an individualised therapy with selection of recombinant or human plasma-derived coagulation Factor-IX products for adults with severe and moderate haemophilia B (congenital Factor IX deficiency) with no history of Factor IX inhibitors, as well as marstacimab and concizumab as comparators for the required routine practice data collection for etranacogene dezaparvovec.

The following criteria were used in the assessment:

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.

Statement on criterion 1: In addition to etranacogene dezaparvovec, the following active ingredients are approved for the therapeutic indication of haemophilia B:

- Recombinant Factor IX products: albutrepenonacog alfa, eftrenonacog alfa, nonacog alfa, nonacog beta pegol and nonacog gamma;
- Human plasma Factor IX products;
- Factor VIII inhibitor bypassing activity enriched human plasma fraction;
- Recombinant coagulation Factor VIIa product: eptacog alfa;
- Monoclonal antibodies: marstacimab, concizumab.

Statement on criterion 2: A non-medicinal treatment cannot be considered a comparator therapy in the therapeutic indication.

Statement on criterion 3: The following resolutions of the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the therapeutic indication "Haemophilia B" are available:

- albutrepenonacog alfa from 1 December 2016 (repealed) and from 7 April 2022,
- eftrenonacog alfa from 15 December 2016 (repealed) and from 1 February 2024,
- nonacog beta pegol from 19 April 2018 and from 15 February 2024,

- etranacogene dezaparvovec from 19 October 2023,
- marstacimab from 17 July 2025,
- concizumab from 16 October 2025 and 19 March 2026.

Statement on criterion 4: Two new medicinal products, marstacimab and concizumab, have been approved for the present therapeutic indication. As part of the respective benefit assessment procedures, the scientific-medical societies have identified marstacimab and concizumab as new and important add-on options for the prophylactic treatment of patients with severe haemophilia B, or with severe and moderate haemophilia B without Factor IX inhibitors. In the overall assessment of the currently available evidence, however, no unanimous therapy recommendation can be derived for the use of marstacimab and concizumab in the present therapeutic indication. As part of the benefit assessment according to Section 35a SGB V, it was found that the additional benefit of marstacimab and concizumab compared with routine prophylaxis with recombinant or human plasma-derived coagulation Factor IX products for adults and adolescents 12 years of age and older with severe haemophilia B (congenital Factor IX deficiency, FIX < 1%) without Factor IX inhibitors, or with severe and moderate haemophilia B (FIX ≤ 2%) without Factor IX inhibitors, is not proven. For the present requirement of routine practice data collection and evaluations, marstacimab and concizumab are defined as a comparator for the routine practice study in addition to the recombinant or human plasma-derived coagulation Factor IX products. The G-BA determine marstacimab and concizumab as a comparator for the routine practice study taking into account the required duration of the routine practice data collection, during which a new situation may arise with regard to the generally recognised state of medical knowledge in the therapeutic indication in question. In principle, this is to be considered separately from the determination of the appropriate comparator therapy, which only becomes legally binding with the resolution on the benefit assessment according to Section 35a, paragraph 3 SGB V.

Taking into account the aspects described, in the overall assessment, the G-BA define an individualised therapy with selection of recombinant or human plasma-derived coagulation Factor IX products as well as marstacimab and concizumab as the comparator for the present routine practice data collection. In accordance with the aforementioned explanations, data on treatment with recombinant or human plasma-derived coagulation Factor IX products as well as marstacimab and concizumab are to be collected for the routine practice data collection according to Section 35a, paragraph 3b, sentence 1 SGB V for the patient population required in this case.

This change is to be implemented within the framework of an addendum to the study protocol and the statistical analysis plan for the RPDC study for the active ingredient etranacogene dezaparvovec in accordance with the VerfO requirements and submitted together with the 2nd interim analysis for review.

The adjustments to the study protocol and the SAP required on the basis of the present change in the comparator are to be submitted to the G-BA by 30 April 2028.

3. Submission according to Section 35a, paragraph 3b, sentences 7 and 8 SGB V

The draft resolution and the justification for the amendment to the requirement of RPDC and evaluations (change in the comparator) were sent to the participants in accordance with

Section 35a, paragraph 3b, sentences 7 and 8 SGB V for written submission. The deadline for making the written submissions was 11 June 2026.

4. 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.

5. Process sequence

Subsequent to the adoption of the resolution of 12 May 2023 on an amendment to the Pharmaceuticals Directive (AM-RL) Annex XII – Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V – etranacogene dezaparvovec, an amendment to the resolution is necessary due to the review of data collection. In addition, this resulted in further development with regard to the generally recognised state of medical knowledge, taking into account the resolutions on the benefit assessment of marstacimab from 17 July 2025 and of concizumab from 19 March 2026: This results in further changes to the G-BA requirements for routine practice data collection and evaluations (change in the comparator).

The issue was discussed in the working group WG RPDC and in the Subcommittee on Medicinal Products.

At their session on 27 May 2026, the Subcommittee unanimously decided on the written submission of participants in the amendment to the requirement of RPDC and evaluations (change in the comparator) in accordance with Section 35a, paragraph 3b, sentences 7 and 8 SGB V.

The evaluation of the written submissions received was discussed at the Subcommittee's session on 23 June 2026, and the draft resolution was approved.

At their session on 2 July 2026, the plenum consensually decided on the amendment to the Pharmaceuticals Directive (AM-RL).

Chronological course of consultation

Session	Date	Subject of consultation
WG RPDC	7 May 2026 18 May 2026 4 June 2026	Consultation on the issue
Subcommittee on Medicinal Products	27 May 2026	Discussion and consensus on the draft resolution on the amendment of the resolution on requirements Initiation of the submission procedure *(change in the comparator)*
WG RPDC	15 June 2026	Evaluation of the written submission *(change in the comparator)*
Subcommittee on Medicinal Products	23 June 2026	Consultation on the amendment to the resolution of 12 May 2023
Plenum	2 July 2026	Adoption of the resolution on the amendment to the resolution of 12 May 2023

Berlin, 2 July 2026

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Dr Optendrenk