Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee 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

At its session on 19 October 2023, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. In Annex XII, the following information shall be added to the information on the restriction of the authority to supply care of Etranacogene dezaparvovec according to the resolution of 12 May 2023 after the explanations on the restriction of the authority to supply care according to Section 35a, paragraph 3b, sentence 2 SGB V:

Etranacogene dezaparvovec

Resolution of: 19 October 2023
Entry into force on: 19 October 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 20 February 2023):

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 therapeutic indication according to marketing authorisation.

1. Extent of the additional benefit and significance of the evidence

Etranacogene dezaparvovec is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5 Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5 Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

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

Extent of the additional benefit and significance of the evidence of etranacogene dezaparvovec:

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

Study results according to endpoints:[1]

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	The data are not assessable.
Morbidity	n.a.	The data are not assessable.
Health-related quality of life	n.a.	The data are not assessable.
Side effects	n.a.	The data are not assessable.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: No data available. n.a.: not assessable		

CT-AMT-061-02 (HOPE-B) study: open-label, single-arm, multicentre phase III study

(2-year data cut-off from 28 February 2022)

Mortality

Endpoint	Etranacogene dezaparvovec	
	N[a)]	Patients Patients with event n (%)
Deaths	54	1 (1.9)

Morbidity

Endpoint	Etranacogene dezaparvovec		
	N[b)]	Number of bleeding events n *Patients with event n (%)*	Annualised bleeding rate (ABR) [95% CI][c)]

[1] Data from the dossier assessment of the G-BA (published on 1. August 2023), and from the amendment (published on 19. Oktober 2023), unless otherwise indicated.

All bleeding events [d)]	54	106 *31 (57.4)*	1.01 [0.67; 1.52]
- Bleeding events treated with exogenous FIX [e)]	54	59 *21 (38.9)*	0.82 [0.46; 1.48]
Bleeding events by bleeding type			
All spontaneous bleeding events	54	31 *15 (27.8)*	0.51 [0.23; 1.12]
- Treated spontaneous bleeding events	54	22 *n.d.*	n.d.
All traumatic bleeding events	54	58 *24 (44.4)*	0.60 [0.34; 1.06]
- Treated traumatic bleeding events	54	24 *n.d.*	n.d.
All joint bleeding events	54	38 *18 (33.3)*	0.52 [0.27; 1.01]
- Treated joint bleeding events	54	30 *n.d.*	n.d.

Endpoint	**Etranacogene dezaparvovec**	
	N[b)]	Patients with event n (%)
No bleeding (between day 22 to month 24 after treatment)	54	23 (43)

Endpoint	**Etranacogene dezaparvovec**			
	Baseline[g)] MV (SD)	N[b)]	Changes to month 24 MV (SD)	Patients with 15% change from month 24 n (%)
Health status				
- EQ-5D-VAS[g)]	80.3 (17.2)	50	3.3 (13.2)	*Improvement:* 5 (10.0) *Deterioration:* 1 (2.0)

Endpoint	**Etranacogene dezaparvovec**		
	Baseline[f)] MV (SD)	N[b)]	Changes to month 24 MV (SD)
Pain using the Brief Pain Inventory - Short Form[h)]			
- Pain severity domain	2.3 (2.2)	47	- 0.4 (1.6)
- Pain interference domain	2.1 (2.7)	46	- 0.6 (2.2)

Functional impairments using the Haemophilia Activities List (HAL)[i)]			
- Upper extremity activities	87.6 (17.9)	50	1.9 (7.9)
- Basic lower extremity activities	74.8 (28.5)	50	3.6 (14.9)
- Complex lower extremity activities	63.7 (32.7)	50	3.6 (13.6)
- HAL total score	78.4 (22.6)	50	3.5 (11.4)

Endpoint	**Etranacogene dezaparvovec**	
	N[b)]	MV (SD)
FIX activity[j)] [% based on normal human plasma] – month 24 after EtranaDez treatment *(presented additionally)*	50	36.7 (19.0)

Health-related quality of life

Endpoint	**Etranacogene dezaparvovec**			
	Baseline[g)] MV (SD)	N[b)]	Changes to month 24 MV (SD)	Patients with 15% change from month 24 n (%)
Quality of life using the Haemophilia Specific Quality of Life Index (Hem-A-QoL)[k)]				
- Total score	26.4 (17.2)	45	- 6.4 (10.8)	*Improvement:* 7 (15.6) *Deterioration:* 1 (2.2)
- Physical health	33.1 (30.9)	48	- 5.5 (23.0)	*Improvement:* 13 (27.1) *Deterioration:* 10 (20.8)
- Feelings	21.0 (25.1)	48	- 9.2 (18.2)	*Improvement:* 13 (27.1) *Deterioration:* 1 (2.1)
- Self-image of the patient	32.9 (22.0)	48	- 2.9 (17.0)	*Improvement:* 15 (31.3) *Deterioration:* 10 (20.8)
- Sports and leisure	44.1 (30.7)	48	- 7.9 (29.0)	*Improvement:* 16 (33.3) *Deterioration:* 9 (18.8)
- Work and school *(Change from month 12)[l)]*	18.6 (22.8)	42	- 6.0 (20.7)	*Improvement:* 8 (19.1) *Deterioration:* 2 (4.8)
- Dealing with haemophilia	20.4 (23.9)	48	4.7 (32.7)	*Improvement:* 11 (22.9) *Deterioration:* 17 (35.4)
- Influence of the treatment	24.1 (14.6)	47	- 10.5 (19.5)	*Improvement:* 22 (46.8) *Deterioration:* 7 (14.9)
- Thoughts about the future	31.0 (23.8)	48	- 8.7 (18.3)	*Improvement:* 13 (27.1) *Deterioration:* 3 (6.3)
- Family planning [m)]	11.1 (18.6)	35	n.d.	n.d.

- Partnership and sexuality	10.3 (18.9)	47	- 0.7 (15.9)	*Improvement:* 8 (17.0) *Deterioration:* 5 (10.6)

Side effects

Endpoint	**Etranacogene dezaparvovec**	
	N[a)]	Patients Patients with event n (%)
Overall rate of adverse events (AEs) *(presented additionally)*	54	54 (100)
Severe AEs	54	11 (20)
Serious AEs (SAEs)	54	14 (26)
AEs which led to premature discontinuation of the study medication	54	1 (2)
Severe AEs with incidence ≥ 5%		
Infections and infestations	54	3 (6)
Serious AEs with incidence ≥ 5%		
Infections and infestations	54	3 (6)
AEs of any severity grade with incidence ≥ 10% (MedDRA system organ class)		
Infections and infestations	54	40 (47)
Musculoskeletal and connective tissue disorders	54	36 (67)
General disorders and administration site conditions	54	30 (56)
Gastrointestinal disorders	54	26 (48)
Injury, poisoning and procedural complications	54	25 (46)
Investigations	54	22 (41)
Nervous system disorders	54	22 (41)
Respiratory, thoracic and mediastinal disorders	54	19 (35)
Vascular disorders	54	12 (22)
Metabolism and nutrition disorders	54	10 (19)
Blood and lymphatic system disorders	54	10 (19)
Skin and subcutaneous tissue disorders	54	9 (17)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	54	6 (11)
Hepatobiliary disorders	54	6 (11)

Psychiatric disorders	54	6 (11)
Adverse events of special interest (regardless of severity grade)		
Unexpected reactions	54	2 (4)
AEs related to the administration procedure of the test preparation	54	6 (11)
Any (re)occurrence of cancer	54	3 (6)
AEs which were associated with a concomitant medication	54	2 (4)
AEs which were related to the failure of the product	54	1 (2)
Suspected or confirmed cases of opportunistic or serious infections that were, in the opinion of the investigator, related to the test preparation	54	0 (0)
AEs that were related to a medical product that was part of the product or used for the application of the product	54	0 (0)

a) Safety population.
b) Full Analysis Set.
c) Negative binomial regression model for repeated measures based on a generalised estimating equation.
d) Including contaminated periods for time at risk in the follow-up period; contaminated period was defined as person time of 5 half-lives after use of an exogenous FIX during the follow-up period.
e) Excluding the contaminated periods for the time at risk in the follow-up period; the bleeding events that occurred during the contaminated period were included in the analysis, but not the person time of the contaminated period.
f) The baseline value was defined as the last value prior to administration of gene therapy that was not within 14 days of a bleeding event. That is, the baseline value can be the value of the final lead-in visit, the lead-in month 4 visit or the lead-in baseline visit. The endpoint was not collected at the visit of gene therapy administration.
g) Scale from 0 to 100. A higher value indicates a better health status.
h) Scale from 0 to 10. A higher value indicates more severe pain.
i) Scale from 0 to 100. A higher value indicates a better condition.
j) According to aPTT single step assay. Blood samples whose blood collection did not take place within 5 half-lives after the use of exogenous factor IX were considered.
k) Scale from 0 to 100. A higher value means a lower quality of life.
l) The percentage of patients in the evaluation at month 24 related to the full analysis set was < 70%. Therefore, the results are not presented.
m) The percentage of patients in the evaluation related to the full analysis set was < 70% at all follow-up times. Therefore, the results are not presented.

Abbreviations used: ABR: annualised bleeding rate; aPTT: activated Partial Thromboplastin Time; EQ-5D-VAS: visual analogue scale of the European Quality of Life 5-Dimension Questionnaire; FIX: coagulation factor IX; HAL: Haemophilia Activities List; Hem-A-QoL: Haemophilia Specific Quality of Life Index; CI: confidence interval; MedDRA:: Medical Dictionary for Regulatory Activities; MV: mean value; N = number of patients evaluated; n = number of patients with (at least one) event; SD: standard deviation; (S)AE: (serious) adverse event

2. Number of patients or demarcation of patient groups eligible for treatment

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

approx. 340 patients

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: 06 September 2023):

https://www.ema.europa.eu/en/documents/product-information/hemgenix-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 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 EMA will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

4. Treatment costs

Annual treatment costs:

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

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Etranacogene dezaparvovec	No data available.

(LAUER-TAXE® last revised: 1 October 2023)

The pharmaceutical company does not disclose any direct costs of the statutory health insurance pursuant to Chapter 5 Section 9, paragraph 7, sentence 3 VerfO and thus does not fulfil its obligation to disclose the treatment costs on the basis of appropriate information. According to Sections 35a, paragraph 1, sentence 3, number 5, 131, paragraph 4, sentences 1 and 2 SGB V, the pharmaceutical company is obliged to inform the G-BA of the treatment costs for the statutory health insurance in order to ensure price transparency within the framework of the guidelines according to Section 92, paragraph 1, sentence 2, number 6 SGB V.

Costs for additionally required SHI services: not applicable

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

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

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

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

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. 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.

II. **The resolution will enter into force on the day of its publication on the website of the G-BA on 19 October 2023.**

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 19 October 2023

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

Prof. Hecken