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
Valoctocogene roxaparvovec (severe haemophilia A)

of 16 March 2023

At its session on 16 March 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 valoctocogene roxaparvovec according to the resolution of 2 February 2023 after the explanations on the restriction of the authority to supply care according to Section 35a, paragraph 3b, sentence 2 SGB V:**

Valoctocogene roxaparvovec

Resolution of: 16 March 2023
Entry into force on: 16 March 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 24 August 2022):

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 therapeutic indication according to marketing authorisation.

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

Valoctocogene roxaparvovec is approved as a medicinal product for the treatment of rare diseases under 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).

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)

Extent of the additional benefit and significance of the evidence of valoctocogene roxaparvovec:

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

Study results according to endpoints:[1]

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)

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 ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

BMN 270-301 study (GENEr8-1): open-label, single-arm, phase III intervention study, data cut-off: 15 November 2021

Mortality

BMN 270-301 study Endpoint	**Valoctocogene roxaparvovec**	
	N[b]	Patients with event n (%)
Overall mortality[a)]	134	1 (0.7)

Morbidity

BMN 270-301 study Endpoint	**Valoctocogene roxaparvovec**	
	N[c]	Patients with event n (%)
Bleeding events (overall study period)[d,e]		
No bleeding (presented additionally)	134	42 (31.3)
No joint bleeding	134	96 (71.6)
No bleeding in the target joint	134	126 (94.0)
No treated bleeding	134	79 (59.0)

[1] Data from the dossier assessment of the G-BA (published on 15. December 2022), and from the amendment to the dossier assessment from 7 February 2023, unless otherwise indicated.

BMN 270-301 study Endpoint	**Valoctocogene roxaparvovec**			
	N[c]	Annual bleeding rate (estimated ABR)[f] [95% CI]		
Annual bleeding rate (overall study period)[d,e]				
All bleeding events (presented additionally)	134	1.45 [1.06; 1.98]		
Joint bleeding	134	0.52 [0.31; 0.86]		
Bleeding in the target joint	134	0.07 [0.03; 0.16]		
Bleeding that is not joint bleeding	134	0.94 [0.70; 1.24]		
Spontaneous bleeding	134	0.45 [0.24; 0.83]		
Bleeding due to trauma	134	0.45 [0.30; 0.69]		
Treated bleeding	134	0.90 [0.57; 1.42]		
	Baseline		Week 104, change compared to baseline	
	N[b]	MV (SD)	N[b]	MV [95% CI]; p value[h]
EQ-5D-5L VAS[g]				
VAS	133	79.8 (15.8)	129	3.4 [1.3; 5.4]; 0.002
	N[b]	LS mean [95% CI]	N[b]	LS mean difference [95% CI]; p value[i]
Haemophilia Activity List (HAL)[g]				
Total score	133	78.59 [75.43; 81.74]	129	3.86 [1.81; 5.91]; 0.0002
	N[c]	Median (min; max) MV (SD)		
Median factor VIII activity by chromogenic analysis (IU/dl) (presented additionally)				
Baseline (last measured value before valoctocogene roxaparvovec infusion)	134	3.2 (0; 178.0) 12.5 (22.7)		
Week 104	134	11.7 (0; 187.1) 22.7 (32.8)		

Health-related quality of life

BMN 270-301 study Endpoint	**Valoctocogene roxaparvovec**			
	Baseline		Week 104, change compared to baseline	
	N[b]	LS mean [95% CI]	N[b]	LS mean difference [95% CI]; p value[i]
Haemo-QoL-A[j]				
Total score	131	75.98 [73.28; 78.69]	130	6.94 [5.34; 8.55]; < 0.0001
Physical functioning	134	70.26 [66.85; 73.67]	131	4.61 [2.42; 6.79]; < 0.0001
Role functioning	133	78.33 [75.58; 81.08]	131	7.50 [5.64; 9.37]; < 0.0001
Worries	133	78.68 [75.09; 82.27]	131	7.16 [4.51; 9.81]; < 0.0001
Consequences of bleeding	134	73.78 [70.46; 77.11]	131	10.11 [7.87; 12.34]; < 0.0001
Emotional impact	133	78.28 [75.22; 81.33]	131	3.15 [0.51; 5.78]; 0.019
Concerns about the treatment	131	76.68 [72.44; 80.93]	130	8.69 [5.85; 11.53]; < 0.0001

Side effects

BMN 270-301 study Endpoint	**Valoctocogene roxaparvovec**	
	N[c]	Patients with event n (%)
Adverse events (AEs, presented additionally)	134	134 (100)
Adverse events CTCAE grade ≥ 3	134	42 (31.3)
Serious adverse events (SAEs)[k]	134	24 (17.9)
AEs with incidence ≥ 10% or more than 10 patients and ≥ 1% according to MedDRA system organ class Preferred term		
Investigations	134	121 (90.3)
ALT increased	134	119 (88.8)
AST increased	134	47 (35.1)
Weight increased	134	22 (16.4)
Elevated creatine phosphokinase level in the blood	134	17 (12.7)
Infections and infestations	134	109 (81.3)

BMN 270-301 study Endpoint	**Valoctocogene roxaparvovec**	
	N[c]	Patients with event n (%)
Upper respiratory tract disorders	134	33 (24.6)
Nasopharyngitis	134	29 (21.6)
Rhinitis	134	12 (9.0)
Folliculitis	134	11 (8.2)
Pustular rash	134	11 (8.2)
Musculoskeletal and connective tissue disorders	134	94 (70.1)
Arthralgia	134	53 (39.6)
Back pain	134	25 (18.7)
Myalgia	134	17 (12.7)
Pain in the extremities	134	16 (11.9)
Gastrointestinal disorders	134	89 (66.4)
Nausea	134	51 (38.1)
Diarrhoea	134	28 (20.9)
Vomiting	134	21 (15.7)
Dyspepsia	134	11 (8.2)
Abdominal malaise	134	10 (7.5)
Pain in the upper abdomen	134	10 (7.5)
General disorders and administration site conditions	134	73 (54.5)
Fatigue	134	40 (29.9)
Fever	134	31 (23.1)
Pain	134	10 (7.5)
Skin and subcutaneous tissue disorders	134	73 (54.5)
Acne	134	36 (26.9)
Rash	134	11 (8.2)
Nervous system disorders	134	72 (53.7)
Headache	134	55 (41.0)
Respiratory, thoracic and mediastinal disorders	134	58 (43.3)
Cough	134	24 (17.9)
Oropharyngeal pain	134	24 (17.9)
Injury, poisoning and procedural complications	134	57 (42.5)
Muscle strain	134	13 (9.7)

BMN 270-301 study Endpoint	**Valoctocogene roxaparvovec**	
	N[c]	Patients with event n (%)
Psychiatric disorders	134	53 (39.6)
Insomnia	134	27 (20.1)
Anxiety	134	11 (8.2)
Metabolism and nutrition disorders	134	33 (24.6)
Eye disorders	134	20 (14.9)
Endocrine disorders	134	19 (14.2)
Cushing's syndrome	134	16 (11.9)
Vascular disorders	134	19 (14.2)
Hypertension	134	16 (11.9)
Blood and lymphatic system disorders	134	14 (10.4)
Renal and urinary disorders	134	14 (10.4)
Cardiac disorders	134	10 (7.5)

[a] Deaths are recorded in the BMN 270-301 study as part of the safety survey.
[b] Subjects with available values.
[c] Total number of patients treated with valoctocogene roxaparvovec.
[d] The follow-up period for the "overall study period" is from the administration of valoctocogene roxaparvovec until the end of the study, until the last visit at the data cut-off for analysis, or until withdrawal from the study (whichever occurs first). The median duration of follow-up after valoctocogene roxaparvovec infusion was 110.9 weeks.
Scale 0 and 100; higher values indicate better health status.
[e] In the subsequently submitted documents, the date of the data cut-off for the results presented could not be identified. It is assumed to be 15.11.2021.
[f] The estimated AR of bleeding events and 95% CI are based on a negative binomial regression, modelling the number of treated bleeding events in the corresponding analysis period (here valoctocogene roxaparvovec infusion until end of post-FVIII prophylaxis) with the analysis period in the offset (repeated within subject).
[g] Scale 0 and 100; higher values indicate better health status (EQ-5D-5L VAS) or less functional impairment (HAL).
[h] p value based on a 2-sided t-test against 0.
[i] Stratified analysis using MMRM with visit (week 4, 12, 26, 52, 76, 104) as independent variable.
[j] Scale 0 and 100; higher values indicate a higher health-related quality of life or less impairment.
[k] Severity grade is done using the CTCAE (v4.03). For AEs that do not have a corresponding CTCAE designation, the study's own criteria for severity grading were used (see chapter 2.3.4 of the benefit assessment). Grade 4 or 5 AEs should always be reported as SAEs according to this grading.

Abbreviations:
CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D-5L-VAS: European Quality of Life 5-Dimension 5-Level Visual Analogue Scale; Haemo-QoL-A: Haemophila-specific Quality of Life Questionnaire for Adults; IU: International Unit; CI: confidence interval; LS: least squares; MMRM: Mixed Model for Repeated Measures; MV: mean value; SD: standard deviation; SAE: serious adverse event; AE: adverse event.

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

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)

Approx. 690 to 800 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 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.

4. Treatment costs

Annual treatment costs:

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)

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Valoctocogene roxaparvovec[2]	€ 2,143,958.40
Additionally required SHI services	incalculable

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 March 2023

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

Medicinal products with the new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients that can be used in a combination therapy with valoctocogene roxaparvovec for the treatment of severe haemophilia A in adults on the basis of the marketing authorisation granted under Medicinal Products Act:

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)

- No active ingredient that can be used in a combination therapy that 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 16 March 2023.

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

[2] Valoctocogene roxaparvovec is administered once.

Berlin, 16 March 2023

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

Prof. Hecken