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: Vosoritide (achondroplasia, ≥ 2 years)

of 18 March 2022

At its session on 18 March 2022, 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. Annex XII shall be amended in alphabetical order to include the active ingredient vosoritide as follows:

Vosoritide

Resolution of: 18 March 2022
Entry into force on: 18 March 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 26 August 2021):

Voxzogo is indicated for the treatment of achondroplasia in patients 2 years of age and older whose epiphyses are not closed. The diagnosis of achondroplasia should be confirmed by appropriate genetic testing.

Therapeutic indication of the resolution (resolution of 18 March 2022):

see therapeutic indication according to marketing authorisation

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

Vosoritide 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 German Social Code, Book Five (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).

Patients 2 years of age and older with achondroplasia and whose epiphyses are not closed

Extent of the additional benefit and significance of the evidence of vosoritide:

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

Study results according to endpoints:[1]

Patients 2 years of age and older with achondroplasia and whose epiphyses are not closed

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No deaths occurred.

[1] Data from the dossier assessment of the G-BA (published on 3. January 2022), and from the amendments (from 23 February 2022 and 2 March 2022), unless otherwise indicated.

Endpoint category	Direction of effect/ risk of bias	Summary
Morbidity	↑	Advantage in "height (z-score)".
Health-related quality of life	↔	No relevant difference for the benefit assessment.
Side effects	↔	No relevant differences for the benefit assessment overall.

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 111-301 study: Vosoritide vs placebo in children and adolescents between 5 and 17 years of age

Mortality

Endpoint	Vosoritide		Placebo		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator [95% CI] p value
Overall survival					
No deaths occurred.					

Morbidity

Endpoint	Vosoritide		Placebo		Intervention vs control	
	N	MV (SD) Median (min; max) LS mean [95% CI]	N	MV (SD) Median (min; max) LS mean [95% CI]	LS mean[b,c] [95% CI] p value	Effect estimator [95% CI]
Change in height (z-score)						
German reference population[a]						

Z-score at baseline MV (SD) Median (min; max)	60	 -5.69 (1.11) -5.84 (-7.7; -1.4)	61	 -5.68 (1.09) -5.51 (-8.4; -3.3)	-	-
Z-score at week 52 Mean value (SD) Median (min; max) LS mean[c,d] [95% CI]	60	 -5.39 (1.11) -5.44 (-7.6; -1.3) 0.28 [0.20; 0.35]	61	 -5.66 (1.05) -5.59 (-8.1; -3.5) -0.01 [-0.09; 0.07]	0.28 [0.19; 0.37] < 0.0001	n.d.
USA reference population						
Z-score at baseline MV (SD) Median (min; max)	60	 -5.13 (1.11) -5.27 (-7.7; -1.1)	61	 -5.14 (1.07) -5.15 (-7.9; -2.7)	-	-
Z-score at week 52 Mean value (SD) Median (min; max) LS mean[c,d] [95% CI]	60	 -4.89 (1.09) -4.86 (-7.5; -1.1) 0.27 [0.18; 0.36]	61	 -5.14 (1.09) -5.11 (-7.8; -2.8) -0.01 [-0.10; 0.09]	0.28 [0.17; 0.39] < 0.0001	Hedges' g 0.76 [0.39; 1.13]
Annualized growth velocity (AGV) [cm/year] (presented additionally)						
AGV to baseline MV (SD) Median (min; max)	60	 4.26 (1.53) 4.14 (-0.1; 6.9)	61	 4.06 (1.20) 4.13 (1.5; 6.7)	-	-
AGV at week 52 Mean value (SD) Median (min; max) LS mean[c,d] [95% CI]	60	 5.61 (1.05) 5.75 (2.3; 8.4) 1.71 [1.40; 2.01]	61	 3.94 (1.07) 3.97 (1.3; 6.5) 0.13 [-0.18; 0.45]	1.57 [1.22; 1.93] < 0.0001	Hedges' g 1.28 [0.89; 1.68]
Ratio of body segments (presented additionally)						
Ratio of upper to lower body segment						
Value at baseline MV (SD) Median (min; max)	60	 1.98 (0.20) 2.01 (1.3; 2.3)	61	 2.01 (0.21) 1.99 (1.5; 2.6)	-	-
Value at week 52 Mean value (SD) Median (min; max) LS mean[c,d] [95% CI]	60	 1.95 (0.20) 1.97 (1.3; 2.3) -0.03 [-0.06; 0.00]	61	 1.98 (0.18) 1.96 (1.6; 2.4) -0.02 [-0.05; 0.01]	-0.01 [-0.05; 0.02]	-

					0.5060	
Ratio of body proportions (presented additionally)						
Ratio of upper to lower arm length						
Value at baseline MV (SD) Median (min; max)	58	 1.08 (0.14) n.d. [0.8; 1.6]	61	 1.05 (0.08) n.d. [0.9; 1.3]	-	-
Value at week 52 Mean value (SD) Median (min; max) LS mean[c,d] [95% CI]	58	 1.09 (0.13) n.d. [0.9; 1.5] 0.02 [-0.01; 0.05]	61	 1.09 (0.09) n.d. [0.9; 1.3] 0.03 [0.00; 0.06]	-0.01 [-0.04; 0.02] 0.5683	-
Ratio of thigh length to knee-to-heel length						
Value at baseline MV (SD) Median (min; max)	58	 0.65 (0.07) n.d. [0.5; 0.8]	61	 0.66 (0.05) n.d. [0.5; 0.8]	-	-
Value at week 52 Mean value (SD) Median (min; max) LS mean[c,d] [95% CI]	58	 0.66 (0.07) n.d. [0.5; 0.8] 0.01 [0.00; 0.03]	61	 0.67 (0.05) n.d. [0.5; 0.8] 0.02 [0.00; 0.04]	-0.01 [-0.02; 0.01] 0.5678	-
Ratio of thigh length to shin length						
Value at baseline MV (SD) Median (min; max)	58	 1.07 (0.13) n.d. [0.8; 1.5]	61	 1.08 (0.11) n.d. [0.9; 1.4]	-	-
Value at week 52 Mean value (SD) Median (min; max) LS mean[c,d] [95% CI]	58	 1.07 (0.13) n.d. [0.9; 1.4] 0.01 [-0.01; 0.04]	61	 1.10 (0.11) n.d. [0.9; 1.4] 0.03 [0.01; 0.06]	-0.02 [-0.05; 0.01] 0.1949	-
Ratio of arm span to height						
Value at baseline MV (SD) Median (min; max)	58	 0.90 (0.06) n.d. [0.8; 1.2]	61	 0.90 (0.04) n.d. [0.8; 1.0]	-	-
Value at week 52 Mean value (SD)	58	 0.90 (0.04)	61	 0.90 (0.04)		

Median (min; max) LS mean[c,d] [95% CI]		n.d. [0.8; 1.0] 0.00 [-0.01; 0.00]		n.d. [0.8; 1.0] 0.00 [0.00; 0.01]	-0.01 [-0.02; 0.00] 0.1226	-

Health-related quality of life

Endpoint	Vosoritide		Placebo		Intervention vs control
	N[h]	MV (SD) Median (min; max) LS mean [95% CI]	N[h]	MV (SD) Median (min; max) LS mean [95% CI]	Magnitude of effect [95% CI] p value[l]
PedsQL[f,g] (self-reported)					
Total value at baseline MV (SD) Median (min; max)	28	74.07 (11.87) 74.46 (50.0; 93.5)	35	75.32 (14.98) 73.91 (42.4; 96.7)	-
Total value at week 52 MV (SD) Median (min; max)	34	75.94 (12.26) 78.81 (45.7; 97.8)	43	71.33 (13.15) 70.65 (47.8; 96.7)	-
Change to baseline at week 52 MV (SD) Median (min; max)	25	0.85 (13.80) 1.09 (-32.6; 34.8)	33	-2.62 (15.06) 0.00 (-39.8; 22.8)	n.d. 0.3726
QoLISSY[f,g] (self-reported)					
Total value at baseline MV (SD) Median (min; max)	30[i]	64.59 (17.57) 66.84 (20.5; 92.0)	36	66.40 (16.05) 66.50 (21.2; 90.6)	-
Total value at week 52 MV (SD) Median (min; max)	36	67.39 (16.41) 69.62 (26.0; 91.3)	44	64.68 (19.14) 67.71 (9.0; 91.3)	-
Change to baseline at week 52 MV (SD) Median (min; max)	26	4.34 (14.42) 0.69 (-15.8; 41.0)	35	-0.88 (19.02) 1.39 (-63.9; 39.2)	n.d. 0.2461

Side effects

Endpoint	Vosoritide		Placebo		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator [95% CI] p value Absolute difference (AD)[e]
Total adverse events (presented additionally)					
	60	59 (98.3)	61	60 (98.4)	-
Serious adverse events (SAE)					
	60	3 (5.0)	61	4 (6.6)	n.d. 1.000[k]
Severe adverse events (CTCAE grade ≥ 3)					
	60	3 (5.0)	61	3 (4.9)	n.d. 1.000[k]
Therapy discontinuation due to adverse events					
	60	1 (1.7)	61	0 (0)	n.d. 0.4959[k]
AEs of special interest (subjects with ≥ 1 event)					
Reaction at the injection site	60	51 (85.0)	61	50 (82.0)	n.d. 0.8074
Hypersensitivity	60	16 (26.7)	61	7 (11.5)	n.d. 0.0389 AD = 15.2%
Hypotension	60	8 (13.3)	61	3 (4.9)	n.d. 0.1258
Fractures	60	1 (1.7)	61	0 (0)	n.d. 0.4959
Change in heart rate	60	0	61	0	-
Avascular necrosis or bone necrosis	60	0	61	0	-

Endpoint	Vosoritide		Placebo		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator [95% CI] p value Absolute difference (AD)[e]
Slipped capital femoral epiphysis (SCFE)	60	0	61	0	-
Algorithmic anaphylaxis[l]	60	n.d.	61	n.d.	n.d.
Frequent AEs (incidence ≥ 10% in one study arm and more than ≥ 5% difference between treatment groups) **MedDRA system organ class** Preferred term					
General disorders and administration site conditions	**60**	**54 (90.0)**	**61**	**50 (82.0)**	-
Reaction at the administration site	60	44 (73.3)	61	29 (47.5)	-
Swelling at the injection site	60	23 (38.3)	61	6 (9.8)	-
Urticaria at the injection site	60	8 (13.3)	61	2 (3.3)	-
Bleeding at the injection site	60	2 (3.3)	61	7 (11.5)	-
Infections and infestations	60	**38 (63.3)**	61	**46 (75.4)**	-
Influenza	60	6 (10.0)	61	3 (4.9)	-
Gastrointestinal disorders	60	**20 (33.3)**	61	**24 (39.3)**	-
Vomiting	60	16 (26.7)	61	12 (19.7)	-
Diarrhoea	60	6 (10.0)	61	2 (3.3)	-

Endpoint	Vosoritide		Placebo		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator [95% CI] p value Absolute difference (AD)[e]
Musculoskeletal and connective tissue disorders	60	**16 (26.7)**	61	**13 (21.3)**	-
Arthralgia[j]	60	9 (15.0)	61	4 (6.6)	-
Ear and labyrinth disorders	60	**11 (18.3)**	61	**8 (13.1)**	-
Earache[j]	60	6 (10.0)	61	3 (4.9)	-
Investigations	60	**8 (13.3)**	61	**3 (4.9)**	-
Hypotension	60	7 (11.7)	61	3 (4.9)	-
Metabolism and nutrition disorders	60	**3 (5.0)**	61	**8 (13.1)**	-
Vitamin D deficiency	60	3 (5.0)	61	7 (11.5)	-

a) Data from module 4 - calculated post hoc.
b) Group difference of changes.
c) ANCOVA with stratification stratum and treatment group as fixed effects and age at baseline, AGV at baseline and height (z-score) at baseline as covariates.
d) Change to baseline during week 52.
e) Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
f) PedsQL: Range of values between 0 to 100 points, with higher values representing a better quality of life.
g) Surveyed among children aged 8 years and older.
h) On study day 1, 37 children in the placebo arm and 29 in the vosoritide arm were ≥ 8 years old. If a child reached his/her 8th birthday during the course of the study, the self-reported questionnaire was recorded at the next study visit.
i) It is unclear why results are reported for 30 children, whereas 29 of them in the study arm were ≥ 8 years old according to the characterisation of the study population.
j) Preferred term was identified a priori as ACH-related. All events of this preferred term are assigned to the underlying disease ACH in the study report.
k) Calculated post hoc according to Fisher exact test (two-sided)
l) t test

Abbreviations used:

ACH = achondroplasia; AD = Absolute Difference; AGV = Annualized Growth Velocity; ANCOVA = Analysis of Covariance; CTCAE = Common Terminology Criteria for Adverse Events; HR = Hazard Ratio; n.d. = no data available; CI = Confidence Interval; LS = Least Square; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients evaluated; n = number of patients with (at least one) event; SMQ = Standard MedDRA Query; PedsQL = Paediatric Quality of Life Inventory; PT = Preferred Term; QoLISSY = Quality of Life in Short Stature Youth Questionnaire; SD = standard deviation; SAE = serious adverse event; AE = adverse event; vs = versus.

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

Patients 2 years of age and older with achondroplasia and whose epiphyses are not closed

approx. 340 – 480 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 Voxzogo (active ingredient: vosoritide) at the following publicly accessible link (last access: 9 February 2022):

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

Treatment with vosoritide may only be initiated and monitored by doctors experienced in the treatment of patients with growth disorders or skeletal dysplasias.

4. Treatment costs

Patients 2 years of age and older with achondroplasia and whose epiphyses are not closed

Annual treatment costs:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Vosoritide	€ 325,137.26

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 1 March 2022)

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 18 March 2022.

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

Berlin, 18 March 2022

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

Prof. Hecken