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 of the Fifth Book of the German Social Code (SGB V)
Voxelotor (haemolytic anaemia in sickle cell disease, monotherapy or combination with hydroxycarbamide, ≥ 12 years)

of 3 November 2022

At its session on 3 November 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 Voxelotor as follows:

Voxelotor

Resolution of: 3 November 2022
Entry into force on: 3 November 2022
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 14 February 2022):

Oxbryta is indicated for the treatment of haemolytic anaemia due to sickle cell disease (SCD) in adults and paediatric patients 12 years of age and older as monotherapy or in combination with hydroxycarbamide.

Therapeutic indication of the resolution (resolution of 3 November 2022):

- See therapeutic indication according to marketing authorisation.

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

Voxelotor 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>Patients 12 years of age and older with haemolytic anaemia due to sickle cell disease</u>

Extent of the additional benefit and significance of the evidence of Voxelotor (with or without hydroxycarbamide):

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

Study results according to endpoints:[1]

Patients 12 years of age and older with haemolytic anaemia due to sickle cell disease

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	↔	No relevant differences for the benefit assessment.
Health-related quality of life	∅	No data available.
Side effects	↔	No relevant differences for the benefit assessment.
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.c.: not calculable		

HOPE study: Voxelotor (with hydroxycarbamide if necessary) **vs** placebo (with hydroxycarbamide if necessary)

Mortality (safety population)

Endpoint	Voxelotor (+ hydroxycarbamide if necessary)		Placebo (+ hydroxycarbamide if necessary)		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[a]
Overall survival					
	88	2 (2)	91	2 (2)	-

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

Morbidity (ITT population)

Endpoint	Voxelotor (+ hydroxycarbamide if necessary)		Placebo (+ hydroxycarbamide if necessary)		Intervention vs control
	N	*Event rate*	N	*Event rate*	Rate ratio [95% CI] p value
Acute Chest Syndrome (ACS) or pneumonia - Annual event rate [b]					
	90	0.19 [c]	92	0.14 [c]	1.34 [0.64; 2.84] 0.441
Vaso-Occlusive Crisis (VOC) - Annual event rate [b]					
	90	2.41 [c]	92	2.80 [c]	0.86 [0.61; 1.22] 0.404

Endpoint	Voxelotor (+ hydroxycarbamide if necessary)		Placebo (+ hydroxycarbamide if necessary)		Intervention vs control
	N	Median time to event in weeks [95% CI] *Patients with event n (%)*	N	Median time to event in weeks [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[a]
Time until the 1st ACS or the 1st pneumonia (presented additionally)					
	90	n.a. [n.c.; n.c.] 15 (17)	92	n.a. [n.c.; n.c.] 14 (15)	1.13 [0.54; 2.33] 0.750
Time until the 1st VOC (presented additionally)					
	90	12.4 [9.3; 20.1] 63 (70)	92	11.6 [8.0; 18.4] 71 (77)	0.86 [0.62; 1.21] 0.402

Health-related quality of life

No data on health-related quality of life were assessed.

Side effects (safety population)

Endpoint	Voxelotor (+ hydroxycarbamide if necessary)		Placebo (+ hydroxycarbamide if necessary)		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value Absolute difference (AD)[a]
Total adverse events (presented additionally) [d]					
	88	85 (97)	91	82 (90)	-
Serious adverse events (SAE) [d]					
	88	25 (28)	91	23 (25)	1.14 [0.69; 1.88] 0.6052
Severe adverse events (CTCAE grade ≥ 3) [d]					
	88	29 (33)	91	34 (37)	0.90 [0.59; 1.38] 0.6276
Therapy discontinuation due to adverse events [d]					
	88	9 (10)	91	6 (7)	1.42 [0.53; 3.76] 0.4826
SAE (incidence ≥ 5%) [d] **SOC**					
Blood and lymphatic system disorders	88	2 (2)	91	5 (6)	0.41 [0.08; 2.08] 0.2836
Infections and infestations	88	6 (7)	91	8 (9)	0.75 [0.27; 2.10] 0.5850
Respiratory, thoracic and mediastinal disorders	88	6 (7)	91	2 (2)	3.10 [0.64; 14.96] 0.1584
Severe AEs (incidence ≥ 5%) [d] **SOC**					
Blood and lymphatic system disorders	88	5 (6)	91	7 (8)	0.74 [0.24; 2.24] 0.5926

Gastrointestinal disorders	88	3 (3)	91	5 (6)	0.62 [0.15; 2.52] 0.5043
General disorders and administration site conditions	88	2 (2)	91	11 (12)	0.19 [0.04; 0.82] 0.0267
Infections and infestations	88	4 (5)	91	11 (12)	0.38 [0.12; 1.14] 0.0831

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] The event rate is calculated by dividing the total number of events by the total number of person-years. The total number of events refers to the time from randomisation to the end of the study, initiation of HU therapy (for subjects without HU therapy at baseline) or withdrawal of consent. The person-years correspond to the total time in the study of all subjects included in the analysis.
[c] negative binomial model, adjusted for the 3 stratification factors at randomisation ("HU therapy at baseline" (yes, no), "region" (North America, Europe, other) and "age" (adolescents [12 to <18 years], adults [18 to 65 years])
[d] Overall rates of AEs excluding events related to the underlying disease ("sickle cell anaemia with crisis" (PT), "acute chest syndrome" (PT), "pneumonia" (including "pneumonia due to mycoplasma" (PT)), "priapism" (PT) as well as "osteonecrosis" (PT)) are presented.

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; n.d.= no data available; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; vs = versus

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

Patients 12 years of age and older with haemolytic anaemia due to sickle cell disease

approx. 1,580 – 2,580 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 Oxbryta (active ingredient: voxelotor) at the following publicly accessible link (last access: 28 September 2022):

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

Treatment with voxelotor should be initiated and monitored by doctors experienced in treating patients with sickle cell disease.

4. Treatment costs

Annual treatment costs:

Patients 12 years of age and older with haemolytic anaemia due to sickle cell disease

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Voxelotor	€ 100,278.28
plus	
Hydroxycarbamide	€ 3,914.26 - € 11,935.50
Total:	€ 100,278.28 - € 112,213.78

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 October 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 3 November 2022.

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

Berlin, 3 November 2022

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

Prof. Hecken