Resolution

Gemeinsamer Bundesausschuss

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
Crizanlizumab (Prevention of vaso-occlusive crises in sickle cell disease)

of the 20th of May 2021

At its session on the 20th of May 2021, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive, (AM-RL) in the version dated the 18th of December 2008/the 22nd of January 2009 (Federal Gazette, BAnz. No. 49a of the 31st of March 2009), as last amended on DD. 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 crizanlizumab as follows:

Crizanlizumab

Resolution of: the 20th of May 2021
Entry into force on: the 20th of May 2021
BAnz AT DD MM JJJJ Bx

Therapeutic indication (according to the marketing authorisation of the 28th of October 2020):

Adakveo is indicated for the prevention of recurrent vaso-occlusive crises (VOCs) in sickle cell disease patients aged 16 years and older. It can be given as an add-on therapy to hydroxyurea/hydroxycarbamide (HU/HC) or as monotherapy in patients for whom HU/HC is inappropriate or inadequate.

Therapeutic indication of the resolution (resolution from the 20/05/2021):

- see therapeutic indication according to marketing authorisation

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

Crizanlizumab 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 the 16th of 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 Ordinance on the Benefit Assessment of Pharmaceuticals (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 16 years and older with sickle cell disease; prevention of recurrent vaso-occlusive crises (VOCs)

Extent of additional benefit and significance of the evidence of crizanlizumab (with or without hydroxyurea):

Hint for a minor additional benefit.

Study results according to endpoints:[1]

Patients 16 years and older with sickle cell disease; prevention of recurrent vaso-occlusive crises (VOCs)

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	↑	Advantage in terms of a reduction or a delay in the occurrence of VOC.
Health-related quality of life	↔	No relevant difference for the benefit assessment.
Side effects	↔	No relevant difference 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.a.: not assessable		

SUSTAIN study: Crizanlizumab with or without hydroxyurea (HU) **vs** placebo with or without HU

Mortality (safety population)

Endpoint	Crizanlizumab (+ HU, if applicable)		Placebo (+ HU, if applicable)		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					
	66	2 (3)	62	2 (3.2)	-

[1]Data from the dossier assessment of the G-BA (published on the 1 March 2021), unless otherwise indicated.

Morbidity (ITT population)

Endpoint	Crizanlizumab (+ HU, if applicable)		Placebo (+ HU, if applicable)		Intervention vs control
	N	Estimated AR VOCs [95% CI]	N	Estimated AR VOCs [95% CI]	Rate ratio [95 % CI] p value
VOCs - annual rate (AR; sensitivity analysis without taking missing values into account) [b, d, e]					
according to CRC PS-1	67	2,43 [1.9; 3.11]	65	3,75 [2.99; 4.71]	0,65 [0.47; 0.9] 0.008

Endpoint	Crizanlizumab (+ HU, if applicable)		Placebo (+ HU, if applicable)		Intervention vs control
	N	MV (SD)	N	MV (SD)	Rate ratio [95 % CI] p value
VOCs - AR (sensitivity analyses with imputation models)					
according to CRC PhS-M6a [e, g]	67	n. d.	65	n. d.	0.74 [0.54; 1.03] n. d.
according to the principal investigator PhS-M6b [e, h]	66		65	-	0.74 [0.52; 1.06] n. d.

Endpoint	Crizanlizumab (+ HU, if applicable)		Placebo (+ HU, if applicable)		Intervention vs control
	N	Median time to event in months [25.; 75. Percentile] *Patients with event n (%)*	N	Median time to event in months [25.; 75. Percentile] *Patients with event n (%)*	Hazard ratio (HR) [95 % CI] p value Absolute difference (AD)[a]
Time to first VOC [i]					
according to CRC	67	4.07 [1.31; n.c.] 43 (64.2)	65	1.38 [0.39; 4.9] 54 (83.1)	0.5 [0.33; 0.74] 0.001 AD ≤ 2.69

Health-related quality of life (ITT population)

Endpoint	Crizanlizumab (+ HU, if applicable)		Placebo (+ HU, if applicable)		Intervention vs control
	N	n (%) MV (SD)	N	n (%) MV (SD)	Mean difference [95% CI] p value
SF-36 (change from start of treatment to week 26)					
Physical component score (PCS)	67	46 (68.7) 0.74 (7.88)	65	46 (70.8) 0.26 (7.46)	0.51 [-2.33; 3.35] 0.723
Mental component score (MCS)	67	46 (68.7) 1.27 (12.41)	65	46 (70.8) 2.44 (11.87)	-0.83 [-5; 3.34] 0.694

Side effects (safety population)

Endpoint	Crizanlizumab (+ HU, if applicable)		Placebo (+ HU, if applicable)		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)					
	66	57 (86.4)	62	55 (88.7)	-
Serious adverse events (SAE)					
	66	17 (25.8)	62	17 (27.4)	0.94 [0.53; 1.67] 0.820
Severe adverse events					
The data are not assessable.					
Therapy discontinuation because of adverse events					
	66	2 (3.0)	62	3 (4.8)	0.63 [0.11; 3.62] 0.595
SAE with incidence ≥ 5 % according to MedDRA system organ classes					
Infections and infestations					
SAE	66	8 (12.1)	62	10 (16.1)	0.75 [0.32; 1.78] 0.512
AE with incidence ≥ 10 % according to MedDRA system organ classes					

Endpoint	Crizanlizumab (+ HU, if applicable)		Placebo (+ HU, if applicable)		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95 % CI] p value Absolute difference (AD)[a]
Blood and lymphatic system disorders	66	8 (12.1)	62	10 (16.1)	0.75 [0.32; 1.78] 0.526
Gastrointestinal disorders	66	26 (39.4)	62	15 (24.2)	1.63 [0.96; 2.77] 0.069
General disorders and administration site conditions	66	24 (36.4)	62	18 (29.0)	1.25 [0.76; 2.07] 0.389
Infections and infestations	66	34 (51.5)	62	33 (53.2)	0.97 [0.70; 1.35] 0.844
Injury, poisoning, and procedural complications	66	10 (15.2)	62	2 (3.2)	4.70 [1.07; 20.59] 0.022
Investigations, examinations	66	14 (21.2)	62	18 (29.0)	0.73 [0.40; 1.34] 0.315
Metabolism and nutrition disorders	66	4 (6.1)	62	9 (14.5)	0.42 [0.14; 1.29] 0.118
Musculoskeletal, connective tissue and bone diseases	66	27 (40.9)	62	18 (29.0)	1.41 [0.87; 2.29] 0.162
Nervous system disorders	66	21 (31.8)	62	15 (24.2)	1.32 [0.75; 2.31] 0.339
Respiratory, thoracic and mediastinal disorders	66	13 (19.7)	62	16 (25.8)	0.76 [0.40; 1.45] 0.419
Skin and subcutaneous tissue disorders	66	12 (18.2)	62	9 (14.5)	1.25 [0.57; 2.76] 0.587

[A] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation

[b] No imputations were made in this analysis. Missing data were not taken into account by extrapolating the available data. Premature study discontinuations affected 24 subjects in each of the two arms. 27 subjects in the crizanlizumab arm and 24 subjects in the placebo arm had ≥ 1 of the reported protocol violations.

[d] The reference period starts at the date of randomisation and ends at the end of treatment, where the end of treatment was defined as the time of the last dose + 14 days. The extent to which VOCs have been annualised is unclear due to contradictory presentations of results. For subjects who never received treatment, end of treatment was defined as the date of study termination (i.e., last contact)

Endpoint	Crizanlizumab (+ HU, if applicable)		Placebo (+ HU, if applicable)		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95 % CI] p value Absolute difference (AD)[a]

[e] Rates and rate ratios including 95% confidence interval and p value estimated using a negative binomial regression model (log-link function) with the logarithm of study duration as offset variable and the number of VOC in the previous year (2-4 vs 5-10), use of concomitant HU therapy (yes vs no), and treatment as independent variables.

[g] An imputation of the number of VOCs was performed for early treatment discontinuation for subjects in the crizanlizumab arm using a jump-to-reference method based on VOCs or uncomplicated VOCs from subjects in the placebo arm. For subjects in the placebo arm, replacement under the missing at random assumption was based on data from subjects in the same study arm before treatment discontinuation.

[h] The approach is methodologically equivalent to PhS-M6a (see footnote g), but based on data on VOCs according to the principal investigator and excluding one individual in the crizanlizumab arm.

[i] Time to first VOC was defined as the time from randomisation to the occurrence of the first VOC (VOC definition according to primary endpoint). If no such event occurred before any study discontinuation or end of treatment (defined as time of last dose + 14 days), censoring was performed at the time of treatment discontinuation or end of treatment. For subjects who never received treatment, end of treatment was defined as the date of study termination (i.e., last contact).

Abbreviations used:
AD = absolute difference; CRC = Crisis Review Committee; CTCAE = Common Terminology Criteria for Adverse Events; HL = Hodges-Lehmann; HR = hazard ratio; HU = hydroxyurea; JR = annual rate; n.d. = no data; 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; PhS = post-hoc sensitivity analysis; PS = prespecified sensitivity analysis; VOCs = vaso-occlusive crises; vs. = vs

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

approx. 390 to 1,690 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 Adakveo (active ingredient: crizanlizumab) at the following publicly accessible link (last access: the 08th of April 2021):

https://www.ema.europa.eu/en/documents/product-information/adakveo-epar-product-information_de.pdf

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

This medicinal product has been authorised under a so-called “conditional approval” scheme. The EMA will assess new information on this medicinal product at least annually and update the product information for healthcare professionals as necessary.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/patient
Crizanlizumab	€ 93,565.68
plus hydroxycarbamide if necessary	€ 11,010.96 – € 25,460.94
Total:	€ 93,565.68 – € 119,026.62

Costs after deduction of statutory rebates (LAUER-TAXE®, as last revised: the 01st of May 2021)

Costs for additionally required SHI services: not applicable

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Crizanlizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	13.0	€ 923

II. Entry into force

1. **The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on the 20th of May 2021.**
2. **The period of validity of the resolution is limited to the 1st of December 2025.**

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

Berlin, 20 May 2021

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

Prof. Hecken