Resolution

Gemeinsamer Bundesausschuss

of the Resolution 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 Burosumab (new therapeutic indication: X-linked hypophosphataemia, ≥ 18 years)

of 15 April 2021

At its session on 14 April 2021, 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 on DD Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of burosumab in accordance with the resolution of 2 April 2020:

Burosumab

Resolution of: 15 April 2021
Entry into force on: 15 April 2021
BAnz AT TT. MM JJJJ Bx

New therapeutic indication (according to the marketing authorisation of 30 September 2020):

CRYSVITA is indicated for the treatment of X-linked hypophosphataemia (XLH), in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease, and in adults.

Therapeutic indication of the resolution (resolution from the 15/04/2021):

CRYSVITA is indicated for the treatment of X-linked hypophosphataemia (XLH) in adults.

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

Burosumab 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 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).

Adult patients with X-linked hypophosphataemia (XLH)

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

Hint for a minor additional benefit.

Study results according to endpoints:[1]

Adult patients with X-linked hypophosphataemia (XLH)

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 walking ability and stiffness
Health-related quality of life	∅	No data available.
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

UX023-CL303 study: RCT (burosumab vs placebo), 24 weeks

Endpoint category Endpoint UX023-CL303 study	Burosumab	Placebo	Burosumab vs placebo
Mortality			
There were no deaths.			

Endpoint category Endpoint UX023-CL303 study	Burosumab		Placebo		Burosumab vs placebo
	N[a]	n (%)	N[a]	n (%)	Effect estimator [95% CI]; p value
Morbidity					
Serum phosphate (presented additionally)					
Subjects with mean serum phosphate levels ≥ 2.5 mg / dL mid-dose cycle[b]	68	63 (92.6)	66	5 (7.6)	n.a. [n.a.]; <0.0001
Subjects with mean serum phosphate levels	68	46 (67.6%)	66	4 (6.1)	no data available

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

Endpoint category Endpoint UX023-CL303 study	Burosumab		Placebo		Burosumab vs placebo
	N[a]	n (%)	N[a]	n (%)	Effect estimator [95% CI]; p value
≥ 2.5 mg / dL end-dose cycle					

Endpoint category Endpoint UX023-CL303 study	Burosumab			placebo			Burosumab vs placebo
	N[a]	Baseline MV (SD)	Change to week 24 LS Mean Difference (SE)	N[a]	Baseline MV (SD)	Change to week 24 LS Mean Difference (SE)	LS Mean Difference [95%-CI]; p Value
Morbidity							
Walking ability by means of 6MWT							
6MWT distance (Meter)[2]	67	356.78 (109.46)	18.19 (7.66)	65	367.42 (103.41)	-1.65 (7.87)	19.83 [4.19; 35.47] 0.0129 *Hedges' g [95%-CI]: 0.424 [0.075; 0.773]*
Stiffness, Physical Function, Pain: Western Ontario and McMaster Universities Osteoarthritis (WOMAC)[c]							
Pain	67	50.7 (18.0)	-7.1 (2.5)	66	48.0 (15.5)	-2.8 (2.8)	-4.4 [-9.3; 0.6] 0.0848
Pain: Brief Pain Inventory- Short Form (BPI-SF)[d]							
Pain intensity	68	5.2 (1.5)	-0.5 (0.2)	66	4.9 (1.5)	-0.1 (0.2)	-0.4 [-0.9; 0.1] 0.0844
Pain impairment	68	5.2 (2.2)	-0.4 (0.2)	66	4.8 (2.2)	-0.3 (0.2)	-0.2 [-0.7; 0.4] 0.5476
Fatigue: Brief Fatigue Inventory (BFI)[e]							
Changes in BFI	68	5.4 (2.0)	0.0 (0.3)	66	4.9 (1.9)	0.0 (0.3)	0.1 [-0.5; 0.6] 0.7912
Disease state Patient Global Impression of Improvement (PGI-I)							
Changes in PGI-I	68	3,2 (0,6)[f]	3,6 (0,2)[g]	66	3,0 (0,8)[f]	3,9 (0,2)[g]	-0.3 [-0.7; 0.2] 0.2035

Endpoint category	Burosumab	placebo	Burosumab vs placebo

[2] Data from the dossier

Endpoint UX023-CL303 study	N[a]	Responder at week 24 n (%)[h]	N[a]	Responder at week 24 n (%)[h]	RR[i] [95% CI]; p value; *ARR[i]* *[95% CI];* *p value*
Morbidity					
Responder analyses for the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) with decrease of ≥ 15 nu[3]					
Pain	68	no data available	66	no data available	no data available
Stiffness	68	21 (30.9)	66	10 (15.2)	RR 0.491 [0.250; 0.962] 0.0403 *ARR 0.421 [0.178; 0.995] 0.0488*
Physical function	68	14 (20.6)	66	11 (16.7)	RR 0.810 [0.397; 1.653] 0.6591 *ARR 0.827 [0.337; 2.028] 0.6792*

Endpoint category Endpoint UX023-CL303 study	Burosumab		placebo		Burosumab vs placebo
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	Effect estimator [95% CI]; p value
Morbidity					
Pain: Brief Pain Inventory- Short Form (BPI-SF)					
Decrease > 15% from baseline to week 24 in BPI-SF Item 3	68	29 (42.6)	66	23 (34.8)	n.a. [n.a.]; <0,3564

Endpoint category Endpoint UX023-CL303 study	Burosumab	placebo	Burosumab vs placebo
Health-related quality of life			
Quality of life was not recorded in the UX023-CL303 study.			

[3] Data from G-BA Amendment

Endpoint category Endpoint UX023-CL303 study	Burosumab		placebo		Burosumab vs placebo
	N[a]	n (%)	N[a]	n (%)	Relative Risk [95%-CI]; p value
Side effects					
EU	68	64 (94.1)	66	61 (92.4)	-[k]
EU NCI-CTCAE-Grades 3 or 4	68	8 (11.8)	66	9 (13.6)	-[l]
SAE	68	2 (2.9)	66	2 (3.0)	-[l]
EU, which led to the discontinuation of the study medication	68	0	66	0	-[m]

MedDRA[k] system organ class, Preferred Term with an incidence of ≥ 10% in one of the study arms and a difference of ≥ 5% between the treatment groups	Burosumab		Placebo		Burosumab vs placebo
	N[a]	n (%)	N[a]	n (%)	Relative Risk [95%-CI]; p value
Infections and infestations Tooth abscess	68	9 (13.2)	66	5 (7.6)	1,7 [0,6; 4,9]; 0,3986[n]
Musculoskeletal, connective tissue and bone diseases	**68**	**25 (36.8)**	**66**	**30 (45.5)**	**-[o]**
Back pain	68	10 (14.7)	66	6 (9.1)	1,6 [0,6; 4,2]; 0,4260[p]
Arthralgia	68	6 (8.8)	66	16 (24.2)	0,4 [0,2; 0,9]; 0.0198[p]
Pain in the extremities	68	5 (7.4)	66	10 (15.2)	0,5 [0,2; 1,3]; 0,1787[p]
Nervous system disorders	**68**	**26 (38.2)**	**66**	**16 (24.2)**	**1,6 [0,9; 2,7]; 0.0954[p]**
Headaches	68	9 (13.2)	66	5 (7.6)	1,7 [0,6; 4,9]; 0,3986[p]
Restless-Leg-Syndrome	68	8 (11.8)	66	4 (6.1)	1,9 [0,6; 6,1]; 0,3657[p]
Investigations, examinations	**68**	**13 (19.1)**	**66**	**8 (12.1)**	**-[o]**
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain	68	1 (1.5)	66	7 (10.6)	0,1 [0.0; 1,1]; 0.0317[p]
Skin and subcutaneous tissue disorders	**68**	**10 (14.7)**	**66**	**6 (9.1)**	**1,6 [0,5; 4,9]; 0,3977[p]**

a) All patients with ≥ 1 dose of study medication. The evaluation was carried out according to the randomised treatment.
b) primary endpoint of the UX023-CL303 study

c) Higher values correspond to greater pain / greater stiffness / reduced physical function.
d) Higher values correspond to higher Pain Intensity/Pain Impairment
e) Higher values correspond to greater fatigue
f) PGI-S with a 4-point scale was used at baseline. Higher values correspond to a greater burden of disease.
g) The PGI-I with a 7-point scale was used for all study visits after baseline. Higher values correspond to deteriorations.
h) Responders are defined as study participants who showed a decrease of at least 15 normalised units (nu) after 24 weeks.
i) Information from the company: The relative risks were calculated using a 2x2 contingency table. The corresponding confidence intervals were calculated using the Chang and Zhang method.
j) Information from the company: The adjusted relative risks and the associated confidence intervals were determined using the method of Zhang and Yu (independent variables: Treatment Group, Brief Pain Inventory (BPI) Mean Pain and Age).
k) Patient relevance of laboratory parameters unclear
l) Due to the different information in the recalculation document and the study report week 24, the presented Relative Risk cannot be taken into account
m) not calculable
n) MedDRA version 18.1
o) Post hoc calculated using a 2 x 2 contingency table without further adjustments
p) Due to the different information in the recalculation document and the study report week 24, the presented Relative Risk cannot be taken into account

Abbreviations:

ARR: Adjusted Relative Risk; BPI-SF: Brief Pain Inventory - Short Form; BFI: Brief Fatigue Inventory; CTCAE: Common Terminology Criteria for Adverse Events; 6MWT: 6-Minute walking test; n.d.: no data; CI: Confidence interval; LS: Least Squares; MedDRA: Medical Dictionary for Regulatory Activities; NCI: National Cancer Institute; nu: normalised units; n.a.: not available; PGI-I: Patient Global Impression of Improvement (RR-I); RR Relative Risk; SD: Standard deviation; SE: Standard error; (S)AE: (serious) adverse event(s); WOMAC: Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Questionnaire

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

Adult patients with X-linked hypophosphataemia (XLH)

approx. 410 to 810 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 Crysvita (active ingredient: burosumab) at the following publicly accessible link (last access: 20 January 2021):

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

Treatment with burosumab should only be initiated and monitored by specialists who are experienced in the treatment of patients with bone diseases.

This medicinal product was approved under “special conditions”. 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:

Adult patients with X-linked hypophosphataemia (XLH)

Designation of the therapy	Annual treatment costs/patient
Burosumab	€ 325,383.89 – € 366,015.78

Costs after deduction of statutory rebates (LAUER-TAXE®, as last revised: 15 March 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
Burosumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	13.0	€ 923.00

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 15 April 2021.

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

Berlin, 15 April 2021

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

Prof. Hecken