Gemeinsamer Bundesausschuss

Burosumab (Reassessment after the Deadline: Hypophosphataemia)

Resolution of: 2 April 2020 valid until: unlimited
Entry into force on: 2 April 2020
Federal Gazette, BAnz AT 28 05 2020 B2

Therapeutic indication (according to the marketing authorisation of 19 February 2018):

CRYSVITA is indicated for the treatment of X-linked hypophosphataemia with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons.

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

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. According to 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).

Children 1 year of age and older and adolescents with growing skeletons with X-linked hypophosphataemia with radiographic evidence of bone disease.

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

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

Study results according to endpoints:[1]

Children 1 year of age and older and adolescents with growing skeletons with X-linked hypophosphataemia with radiographic evidence of bone disease.

Results of the UX023-CL301 study (RCT, week 64): Burosumab vs conventional therapy (oral phosphate and active vitamin D)

Endpoint category **Endpoint** **Study UX023-CL301**	**Burosumab**	**Conventional therapy**	**Burosumab vs conventional therapy**
Mortality			
No deaths occurred.			

Endpoint category **Endpoint** **Study UX023-CL301**	**Burosumab**		**Conventional therapy**		**Burosumab vs conventional therapy**
	N	**LS Mean (SE)**	**N**	**LS Mean (SE)**	**LS mean difference [95% CI];** **p value**
Morbidity					
Rickets symptomatology by means of Radiographic Global Impression of Change (RGI-C) (ad)[2]					
RGI-C Change at week 64	29	2.06 (0.072)	32	1.03 (0.136)	1.02 [0.72; 1.33]; < 0.0001 *Hedges' g [95% CI]: 1.600 [1.023; 2.178]*

[1] Data from the dossier evaluation by the G-BA (published on 2 January 2020) unless otherwise indicated.

[2] Data from the dossier

Endpoint category Endpoint Study UX023-CL301	Burosumab				Conventional therapy				Burosumab vs conventional therapy
	N	Baseline MD (SD)	Week 64 MD (SD)	LS Mean (SE)	N	Baseline MD (SD)	Week 64 MD (SD)	LS Mean (SE)	LS mean difference [95% CI]; p value (Hedges' g [95% CI])
Morbidity									
Rickets symptomatology by means of Rickets Severity Scale (RSS) (additionally shown)[2]									
RSS	29	3.17 (0.975)	0.95 (0.724)	−2.23 (0.117)	32	3.19 (1.141)	2.17 (0.947)	−1.02 (0.151)	−1.21 [−1.59; −0.83]; < 0.0001 *Hedges' g [95% CI]: −1.119 [−1.710; −0.529]*
Serum phosphate(additionally shown)[2]									
Serum phosphate (mg/dl)	29	2.42 (0.244)	3.36 (0.365)	0.98 (0.061)	32	2.30 (0.257)	2.56 (0.300)	0.24 (0.058)	0.74 [0.58; 0.91]; < 0.0001 *Hedges' g [95% CI]: 1.981 [1.368; 2.595]*

Endpoint category Endpoint Study UX023-CL301	Burosumab			Conventional therapy			Burosumab vs conventional therapy
	N	Baseline	Change at week 64	N	Baseline	Change at week 64	LS mean difference [95% CI]; p value
		MV (SD)	LS Mean (SE)		MV (SD)	LS Mean (SE)	
Morbidity							
Anthropometric parameters - body size: Standing height/lying length (z-score)[b)]							
Standing height/lying length (z-score)	28	−2.3 (1.2)	0.2 (0.1)	32	−2.1 (0.9)	0.0 (0.0)	0.1 [0.0; 0.3]; 0.0490[c)] *Hedges' g [95% CI]: 0.5 [−0.03; 1.0]*
Walking ability by means of 6MWT[b), e)]							
6MWT distance (metres)	15	365.9 (118.1)	79.0 (11.4)	20	450.5 (106.4)	35.8 (16.7)	43.2 [2.3; 84.1]; 0.0383[d)] *Hedges' g [95% CI]: 0.8 [0.1; 1.5]*
Percentage of the expected 6MWT distance	15	62.1 (18.6)	9.6 (1.9)	20	76.2 (14.8)	3.4 (2.8)	6.2 [−0.7; 13.2]; 0.0781
Pain, physical function and fatigue by means of the Patient-Reported Outcomes Measurement Information System (PROMIS)[b), e)]							
Paediatric Pain Interference domain T score[f)]	15	53.1 (11.0)	−3.6 (1.9)	20	49.9 (12.1)	−1.3 (1.3)	−2.3 [−6.6; 2.1]; 0.3091
Physical function mobility domain T score[f)]	15	45.2 (9.1)	2.8 (1.6)	20	45.5 (9.9)	0.9 (1.0)	1.9 [−1.8; 5.6]; 0.3145
Fatigue domain T score[f)]	15	48.8 (9.6)	−3.7 (2.1)	20	47.0 (13.7)	−2.6 (1.5)	−1.1 [−6.2; 4.1]; 0.6810
Pain intensity by means of Faces Pain Scale-Revised (FPS-R)[b), e)]							
FPS-R value[g)]	15	0.4 (1.1)	0.0 (0.3)	19	0.6 (1.2)	0.0 (0.2)	0.1 [−0.6; 0.7]; 0.8786
Quality of life							
No usable data							

Endpoint category Endpoint Study UX023-CL301	Burosumab		Conventional therapy		Relative risk [95% CI]; p value
	N	n (%)	N	n (%)	
Side effects					
AE	29	29 (100)	32	27 (84.4)	-
AE CTCAE grade ≥ 3	29	4 (13.8)	32	3 (9.4)	1.5 [0.3; 7.6]; 0.6988 [h)]
SAE	29	3 (10.3)	32	3 (9.4)	1.1 [0.2; 6.0]; 1.0000 [h)]
AE that led to discontinuation of the study medication	29	0	32	0	-

Study UX023-CL301 MedDRA System Organ Class[i)] Preferred Term with an incidence ≥ 10% in one of the study arms and a difference of ≥ 10% between the treatment groups	Burosumab		Conventional therapy	
	N	n (%)	N	n (%)
General disorders and administration site conditions	**29**	**25 (86.2)**	**32**	**8 (25.0)**
Fever	29	16 (55.2)	32	6 (18.8)
Erythema at the injection site	29	9 (31.0)	32	0
Reaction at the injection site	29	7 (24.1)	32	0
Pruritus at the injection site	29	3 (10.3)	32	0
Swelling at the injection site	29	3 (10.3)	32	0
Rash at the injection site	29	3 (10.3)	32	0
Gastrointestinal disorders	**29**	**23 (79.3)**	**32**	**17 (53.1)**
Vomiting	29	12 (41.4)	32	8 (25.0)
Dental cavities[j)]	29	9 (31.0)	32	2 (6.3)
Diarrhoea	29	7 (24.1)	32	2 (6.3)
Constipation	29	5 (17.2)	32	0
Toothache[j)]	29	4 (13.8)	32	1 (3.1)
Infections and infestations Tooth abscess[j)]	29	8 (27.6)	32	3 (9.4)
Respiratory, thoracic, and mediastinal disorders	**29**	**21 (72.4)**	**32**	**9 (28.1)**
Coughing	29	15 (51.7)	32	6 (18.8)
Rhinorrhoea	29	7 (24.1)	32	2 (6.3)

Study UX023-CL301 **MedDRA System Organ Class**[i)] Preferred Term with an incidence ≥ 10% in one of the study arms and a difference of ≥ 10% between the treatment groups	**Burosumab**		**Conventional therapy**	
	N	**n (%)**	**N**	**n (%)**
Nasal congestion	29	5 (17.2)	32	1 (3.1)
Oropharyngeal pain	29	5 (17.2)	32	1 (3.1)
Asthma	29	4 (13.8)	32	1 (3.1)
Musculoskeletal and connective tissue disorders[j)]	**29**	**17 (58.6)**	**32**	**15 (46.9)**
Arthralgia	29	13 (44.8)	32	10 (31.3)
Nervous system disorders	**29**	**12 (41.4)**	**32**	**9 (28.1)**
Headaches	29	10 (34.5)	32	6 (18.8)
Skin and subcutaneous tissue disorders	**29**	**11 (37.9)**	**32**	**4 (12.5)**
Injury, poisoning, and procedural complications	**29**	**10 (34.5)**	**32**	**2 (6.3)**
Contusion	29	4 (13.8)	32	0
Fall	29	3 (10.3)	32	0
Ear and labyrinth disorders	**29**	**6 (20.7)**	**32**	**3 (9.4)**
Earache	29	4 (13.8)	32	1 (3.1)
Investigations	**29**	**8 (27.6)**	**32**	**4 (12.5)**
Vitamin D reduced	29	6 (20.7)	32	1 (3.1)
Metabolism and nutrition disorders	**29**	**6 (20.7)**	**32**	**3 (9.4)**
Vitamin D deficiency	29	5 (17.2)	32	1 (3.1)

a) Primary endpoint of the Study UX023-CL301
b) All randomised patients met the conditions of the FAS population so that the FAS population corresponds to the ITT population.
c) No baseline information was available for 1 child in the burosumab arm.
d) According to the study report, data were missing for 2 children of the burosumab arm: One child did not complete the 6MWT at baseline, and one child did not complete it at week 40. According to SAP, missing values were treated as such.
e) Was used exclusively in children who were at least 5 years old at the time of the screening round.
f) T-score = standardised score with a mean of 50 and a standard deviation of 10.
g) No baseline information was available for one child in the control arm. According to SAP, missing values were treated as such.
h) Information from Module 4 of the manufacturer's dossier
i) MedDRA Version 18.1
j) may contain events from the morbidity endpoint category

Abbreviations:

Study UX023-CL301 **MedDRA System Organ Class**[i)] Preferred Term with an incidence ≥ 10% in one of the study arms and a difference of ≥ 10% between the treatment groups	**Burosumab**		**Conventional therapy**	
	N	**n (%)**	**N**	**n (%)**
CTCAE: Common Terminology Criteria for Adverse Events; FAS: Full Analysis Set; ITT: Intention to treat; CI: confidence interval; LS: least squares; 6MWT: MedDRA: Medical Dictionary for Regulatory Activities; 6 minute walk test; MV: mean value; RSS: Rickets Severity Scale SAP: statistical analysis plan; RR: relative risk; SD: standard deviation; SE: standard error; PROMIS: Patient-Reported Outcomes Measurement Information System; FPS-R: Faces Pain Scale - Revised; (S)AE: (serious) adverse event(s).				

Summary of results for relevant clinical endpoints

Endpoint category	**Direction of effect/ Risk of bias**	**Summary**
Mortality	↔	No differences relevant for the benefit assessment.
Morbidity	↑	Advantage in motor function (6MWT)
Health-related quality of life	n.a.	No usable data on quality of life were provided.
Side effects	↔	No differences relevant for the benefit assessment.
Explanations: ↑: positive statistically significant and relevant effect with low/unclear reliability of data ↓: negative statistically significant and relevant effect with low/unclear reliability of data ↑↑: positive statistically significant and relevant effect with high reliability of data ↓↓: negative statistically significant and relevant 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		

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

Children 1 year of age and older and adolescents with growing skeletons with X-linked hypophosphataemia with radiographic evidence of bone disease.

approx. 200–500 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: 6 February 2020):
https://www.ema.europa.eu/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 metabolic disorders.

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

Children 1 year of age and older and adolescents with growing skeletons with X-linked hypophosphataemia with radiographic evidence of bone disease.

Designation of the therapy	Annual treatment costs/patient
Burosumab	€ 81,796.10 – 734,847.07

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 March 2020

Costs for additionally required SHI services: not applicable

Other services covered by SHI funds:

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	26.1	€ 1853.10

II. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 2 April 2020.

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

Berlin, 2 April 2020

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

Prof. Hecken