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 Burosumab (exceeding € 50 million turnover limit: X-linked hypophosphataemia, ≥ 1 to ≤ 17 years)

of 21 July 2022

At its session on 21 July 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 is amended as follows:

1. **The information on burosumab in the version of the resolution of 2 April 2020 (Federal Gazette, BAnz AT 28.05.2020 B2) is repealed.**
2. **Annex XII shall be amended in alphabetical order to include burosumab as follows:**

Burosumab

Resolution of: 21 July 2022
Entry into force on: 21 July 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 19.02.2018 and 30 September 2020):

Crysvita is indicated for the treatment of X-linked hypophosphataemia in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease.

Therapeutic indication of the resolution (resolution of 21 July 2022):

see therapeutic indication according to marketing authorisation

a) Additional benefit of the medicinal product in relation to the appropriate comparator therapy

Children and adolescents aged 1 to ≤ 17 years with X-linked hypophosphatemia (XLH) with radiographic evidence of bone disease

Appropriate comparator therapy:

- a phosphate replacement and active vitamin D (calcitriol or alfacalcidol) in combination

Extent and probability of the additional benefit of burosumab over phosphate replacement and active vitamin D in combination:

Hint for a non-quantifiable additional benefit

Study results according to endpoints:[1]

Children and adolescents aged 1 to ≤ 17 years with X-linked hypophosphatemia (XLH) with radiographic evidence of bone disease

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant differences for the benefit assessment.
Morbidity	↑	Advantage in motor function (6MWT)
Health-related quality of life	n.a.	No assessable data on quality of life were presented.
Side effects	↔	No relevant differences for the benefit assessment. In detail, disadvantages with specific AEs.

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

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A22-11) unless otherwise indicated.

UX023-CL301 study (open-label RCT, week 64): Burosumab vs phosphate replacement and active vitamin D in combination

UX023-CL301 study (Week 64) Endpoint category Endpoint	Burosumab		Phosphate replacement + active vitamin D		Burosumab vs phosphate replacement + active vitamin D
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a)]
Mortality					
Overall mortality[b)]	29	0 (0)	32	0 (0)	n. c.
Morbidity					
Dental events[c)]	29	15 (51.7)	32	10 (31.3)	1.66 [0.89; 3.09]; 0.122

UX023-CL301 study (Week 64) Endpoint category Endpoint	Burosumab			Phosphate replacement + active vitamin D			Burosumab vs phosphate replacement + active vitamin D
	N[d)]	Values at the start of the study MV (SD)	Change at the end of the study MV (SE)[i]	N[d)]	Values at the start of the study MV (SD)	Change at the end of the study MV (SE)[i]	MD [95% CI]; p value
Morbidity							
Walking ability (6MWT)[f)]	15	365.9 (118.1)	97.9 (19.3)	20	450.5 (106.4)	30.8 (18.1)	43.20 [2.33; 84.07]; 0.038
Physical functioning/mobility (PROMIS Paediatric Physical Function Mobility Domain Score)[g), h)]							
External assessment, age 5-7 years[i)]	7	42.9 (9.5)	2.6 (3.8)	9	41.9 (11.3)	1.1 (1.6)	0.93 [−5.32; 7.17]; 0.771
Self-assessment, age 8-12 years[i)]	8	47.7 (8.4)	3.0 (1.2)	11	48.4 (7.9)	0.7 (1.3)	2.09 [−0.76; 4.94]; 0.150
Fatigue (PROMIS Paediatric Fatigue Domain Score)[g), j)]							
External assessment, age 5-7 years[i)]	7	51.9 (10.7)	−5.2 (3.7)	9	53.0 (16.2)	−3.3 (3.1)	−1.85 [−9.48; 5.77]; 0.634
Self-assessment, age 8–12 years[i)]	8	45.2 (7.3)	−2.1 (3.1)	11	42.1 (9.4)	−1.0 (2.3)	0.57 [−5.36; 6.49]; 0.852
Pain (PROMIS Paediatric Pain Interference Domain Score)[g), j)]							
External assessment, age 5-7 years[i)]	7	55.9 (12.7)	−4.8 (4.9)	9	52.3 (12.3)	−0.8 (1.7)	−1.52 [−7.56, 4.52]; 0.622
Self-assessment, age 8–12 years[i)]	8	50.0 (8.3)	−3.0 (2.6)	11	47.9 (12.1)	−0.2 (2.6)	−1.64 [−7.06; 3.79]; 0.554
Pain intensity (FPS-R)[j)]							

UX023-CL301 study (Week 64) Endpoint category Endpoint	Burosumab			Phosphate replacement + active vitamin D			Burosumab vs phosphate replacement + active vitamin D
	N[d)]	Values at the start of the study MV (SD)	Change at the end of the study MV (SE)[i]	N[d)]	Values at the start of the study MV (SD)	Change at the end of the study MV (SE)[i]	MD [95% CI]; p value
Self-assessment, age ≥ 5 years	15	0.4 (1.1)	0.1 (0.4)	20	0.7 (1.2)	−0.1 (0.3)	0.05 [−0.58; 0.68]; 0.879
Body height (Z score)	28	-2.32 (1.17)	0.17 (0.07)	32	-2.05 (0.87)	0.02 (0.04)	0.14 [0.00; 0.29]; 0.049

UX023-CL301 study (Week 64) Endpoint category Endpoint	Burosumab				Phosphate replacement + active vitamin D				Burosumab vs phosphate replacement + active vitamin D
	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									
Serum phosphate (presented additionally)[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]*

[2] Data from the dossier

UX023-CL301 study (Week 64) Endpoint category Endpoint	Burosumab		Phosphate replacement + active vitamin D		Burosumab vs phosphate replacement + active vitamin D
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a)]
Health-related quality of life					
No usable data available					
Side effects					
AEs (presented additionally)	29	29 (100)	32	27 (84.4)	–
SAEs	29	3 (10.3)	32	3 (9.4)	1.10 [0.24; 5.04][k)]; 0.971
Severe AEs[l)]	29	4 (13.8)	32	3 (9.4)	1.47 [0.36; 6.03][k)]; 0.637
Discontinuation due to AEs	29	0 (0.0)	32	0 (0.0)	n. c.
Constipation (PT, AEs)	29	5 (17.2)	32	0 (0.0)	12.10 [0.70; 209.71]; 0.016
General disorders and administration site conditions (SOC, AEs)[m)]	29	25 (86.2)	32	8 (25.0)	3.45 [1.86; 6.39]; < 0.001
Injury, poisoning and procedural complications (SOC, AEs)[n)]	29	10 (34.5)	32	2 (6.3)	5.52 [1.32; 23.12]; 0.006
Respiratory, thoracic and mediastinal disorders (SOC, AEs)	29	21 (72.4)	32	9 (28.1)	2.57 [1.42; 4.68]; < 0.001

UX023-CL301 study (Week 64) Endpoint category Endpoint	Burosumab		Phosphate replacement + active vitamin D		Burosumab vs phosphate replacement + active vitamin D
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a)]

a) IQWiG calculation, unconditional exact test (CSZ method)
b) Fatalities were recorded as part of the adverse events.
c) Caries and dental abscesses are the main underlying events.
d) Number of patients who were taken into account in the evaluation for calculating the effect estimate; the values at start of study can be based on other patient numbers.
e) Refers to the change from the start of the study to week 64.
f) Measurement in metres. The 6MWT was only conducted in the age group of 5 years and above.
g) PROMIS scores are presented as T-values. The T-score scales the domain raw score in a standardised score with a mean of 50 and a standard deviation (SD) of 10.
h) Higher (increasing) values mean better symptomatology; positive effects mean an advantage for the intervention.
i) Age at the time of enrolment; in the survey by means of external assessment, the sample size decreases from 8 to 7 (from the start of the study till its -end). However, in the self-assessment survey, the sample size increases from 7 to 8. This is not comprehensible since children who turned 8 years old during the study period should continue to be assessed by their parents.
j) Lower (decreasing) values mean better symptomatology; negative effects mean an advantage for the intervention.
k) IQWiG calculation of RR and 95% CI (asymptotic)
l) Operationalised as CTCAE grade 3 to 4
m) The main underlying events are erythema at the injection site (burosumab: 9 [31.0%], phosphate replacement + active vitamin D: 0 [0.0%]; RR: 20.90; 95% CI: [1.27; 343.87]; p < 0.001) and fever (burosumab: 16 [55.2%], phosphate replacement + active vitamin D: 6 [18.8%]; RR: 2.94; 95% CI: [1.33; 6.50]; p = 0.003)
n) The main underlying events are contusion (burosumab: 4 [13.8%], phosphate replacement + active vitamin D: 0 [0.0%]; RR: 9.90; 95% CI: [0.56; 176.29]; p = 0.030) and fall (burosumab: 3 [10.3%], phosphate replacement + active vitamin D: 0 [0.0%]; RR: 7.70; 95% CI: [0.41; 143.00]; p = 0.072

Abbreviations:
CTCAE: Common Terminology Criteria for Adverse Events; 6MWT: 6-minute walking test; FPS-R: Faces Pain Scale - Revised; GEE: Generalised Estimation Equation; CI: confidence interval; MD: mean difference; MV: mean value; n.c.: not calculable; n: number of patients with (at least 1) event; N: Number of patients evaluated; PROMIS: Patient-Reported Outcomes Measurement Information System; PT: preferred term; RCT: randomised controlled trial; RR: relative risk; RSS: Rickets Severity Score; SD: standard deviation; SE: standard error; SOC: system organ class; SAE: serious adverse event; AE: adverse event

b) Number of patients or demarcation of patient groups eligible for treatment

Children and adolescents aged 1 to ≤ 17 years with X-linked hypophosphatemia (XLH) with radiographic evidence of bone disease

approx. 200 - 550 patients

c) 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: 5 May 2022):

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

Treatment with burosumab should only be initiated and monitored by doctors experienced in the therapy of metabolic bone diseases.

This medicinal product was authorised under "special conditions". The EMA will assess new information on this medicinal product at least annually and update the product information as necessary.

d) Treatment costs

Annual treatment costs:

Children and adolescents aged 1 to ≤ 17 years with X-linked hypophosphatemia (XLH) with radiographic evidence of bone disease

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Burosumab	€ 69,931.56 - € 628,026.29
Appropriate comparator therapy:	
Phosphate replacement and active vitamin D (calcitriol or alfacalcidol) in combination	
Phosphate	incalculable
Active vitamin D	
Calcitriol	€ 148.66 - € 1,031.34
or	
Alfacalcidol	€ 190.82 - € 1,157.49
	Total

Designation of the therapy	Annual treatment costs/ patient
Phosphate + calcitriol	incalculable
Phosphate + alfacalcidol	incalculable

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

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	26.1	€ 1,853.10

The resolution will enter into force on the day of its publication on the website of the G-BA on 21 July 2022.

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

Berlin, 21 July 2022

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

Prof. Hecken