Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) 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

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

Burosumab (Crysvita) was listed for the first time on 15 April 2018 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices. Crysvita for the treatment of X-linked hypophosphataemia (XLH) is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

At its session on 2 April 2020, the G-BA decided on the benefit assessment of burosumab in the therapeutic indication "for the treatment of X-linked hypophosphataemia (XLH) in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease" according to Section 35a SGB V.

If the sales of the orphan drug through the statutory health insurance at pharmacy sales prices and outside the scope of SHI-accredited medical care, including value-added tax, exceed an amount of €50 million in the last twelve calendar months, the pharmaceutical company must

submit evidence in accordance with Section 5, paragraphs 1 to 6 within three months of being requested to do so by the Federal Joint Committee, and in this evidence must demonstrate the additional benefit compared to the appropriate comparator therapy.

By letter dated 21 October 2021, the pharmaceutical company was requested to submit a dossier for the benefit assessment according to Section 35a SGB V by 1 February 2022, due to exceeding the €50 million turnover limit within the period from August 2020 to July 2021. The pharmaceutical company has submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph1, number 6 VerfO on 31 January 2022.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 2 May 2022 on the website of the G-BA (http://www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of burosumab compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods[1] was not used in the benefit assessment of burosumab.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

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

2.1.1 Approved therapeutic indication of burosumab (Crysvita) in accordance with the product information

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 21.07.2022):

see therapeutic indication according to marketing authorisation

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Appropriate comparator therapy for burosumab:

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

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. In addition to burosumab, the following medicinal products are approved in the present therapeutic indication: Phosphate, calcitriol and alfacalcidol.

As XLH is a familial hypophosphataemic rickets, the use of active vitamin D (active ingredients calcitriol and alfacalcidol) is approved for the present indication.

on 2. A non-medicinal treatment paid by the SHI is not considered as an appropriate comparator therapy in the present therapeutic indication for the treatment of XLH.

on 3. For the patient group to be considered in the present therapeutic indication, there are no resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V.

Approved exceptions to the legal prescription exclusion according to Section 34, para. 1, sentence 2 SGB V (OTC overview) according to Annex I of the AM-RL are: "*38. Phosphate compounds in hypophosphataemia that cannot be remedied by appropriate nutrition*".

on 4. The generally state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is

presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The Haffner *et al.* 2019 guideline was included in the evidence synopsis for the treatment of XLH . This guideline provides recommendations for the treatment of children and adults with XLH.

The guideline recommends a phosphate replacement and the additional administration of active vitamin D (calcitriol or alfacalcidol) as medicinal therapy for children and adolescents, especially to avoid secondary hyperparathyroidism.

Based on the available evidence, a phosphate replacement and active vitamin D (calcitriol or alfacalcidol) in combination are determined as the appropriate comparator therapy in the present therapeutic indication for the treatment of "children and adolescents aged 1 to ≤ 17 years with XLH with radiographic evidence of bone disease".

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of burosumab is assessed as follows:

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

Hint for a non-quantifiable additional benefit

Justification:

For the assessment of the additional benefit of burosumab for the treatment of X-linked hypophosphatemia (XLH) in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease, the pharmaceutical company submitted the pivotal, multicentre, randomised, open-label phase III UX023-CL301 study with a data cut-off at week 64.

In the UX023-CL301 study, burosumab was compared to conventional therapy (consisting of oral phosphate and active vitamin D).

The UX023-CL301 study enrolled paediatric patients aged 1 to 12 years with radiographic evidence of XLH and a Rickets Severity Score (RSS) of at least 2.

The marketing authorisation population of 13-17-year-olds was not enrolled in the submitted UX023-CL301 study. For adolescents aged 13-17 years, no data were provided by the pharmaceutical company.

At the time of enrolment, patients had to have a serum phosphate value (fasting value) below 3.0 mg/dl. A PHEX mutation or a variant of unclear significance had to be present in the patient or a directly related family member with corresponding X-linked inheritance. All patients received conventional therapy with oral phosphate and active vitamin D for at least 12

consecutive months (for children ≥ 3 years) or for at least 6 consecutive months (for children < 3 years) until 7 days before randomisation (wash-out phase) prior to enrolment in the study. After the screening phase, patients were randomised to study arms according to rickets severity (RSS total score ≤ 2.5 vs > 2.5), age (< 5 vs ≥ 5 years) and region (Japan vs rest of the world). 29 patients were randomised to the intervention arm (burosumab) and 32 patients to the comparator arm (phosphate replacement + active vitamin D).

The planned treatment duration of the UX023-CL301 study was 64 weeks. Following the study, patients were able to participate in an extension phase of up to 76 weeks, during which all study participants received burosumab. The single-arm extension study is not considered for the present benefit assessment due to the lack of comparison with the appropriate comparator therapy.

The treatment with burosumab in the intervention arm was carried out according to the requirements in the product information. In the UX023-CL301 study, a dose increase of burosumab was only possible up to a maximum of 1.2 mg/kg body weight and not 2 mg/kg body weight as stated in the product information. Concomitant treatment with conventional therapy was contraindicated in the intervention arm. In the control arm, the dosage of oral phosphate and active vitamin D was patient-individual at the doctor's discretion.

The primary endpoint of the UX023-CL301 study was the assessment of "rickets symptoms by Radiographic Global Impression of Change (RGI-C)". Apart from the primary endpoint, endpoints of the categories mortality, morbidity, quality of life and side effects were collected in the UX023-CL301 study.

Extent and probability of the additional benefit

Mortality

There were no deaths in the UX023-CL301 study.

Morbidity

Rickets symptomatology by Radiographic Global Impression of Change (RGI-C) and Rickets Severity Scale (RSS)

In the UX023-CL301 study, rickets symptomatology were assessed using the RGI-C score (primary endpoint) and the Rickets Severity Scale (RSS) as endpoint.

There are no data to support the validity of the RGI-C and RSS as surrogates for morbidity in the present therapeutic indication. Therefore, a patient relevance cannot be derived.

Serum phosphate

The increase of the pathologically decreased serum phosphate value until it reaches the normal range is the clinically important parameter as a therapeutic goal.

Since the extent of an increase in the pathologically low serum phosphate level is not directly associated with the extent of the change in symptomatology, the endpoint is considered additionally. With regard to the patient relevance of the endpoint, there are different opinions within the G-BA.

For the endpoint of serum phosphate level, the UX023-CL301 study showed a statistically significant advantage of burosumab over phosphate replacement and active vitamin D.

The results of serum phosphate show that the serum phosphate level reached the normal range during therapy with burosumab and the pathologically altered serum phosphate level caused by the genetic defect was stabilised.

Motor function: 6-minute walking test (6MWT)

The 6MWT is a standardised and established instrument for determining physical resilience (walking distance that the patient can cover within 6 minutes).

Walking ability was assessed in UX023-CL301 study using the 6MWT in children who were at least 5 years old at baseline. The measurement of the patient's physical resilience or coping with activities of daily living is basically a patient-relevant endpoint.

In the UX023-CL301 study, a statistically significant advantage of burosumab over phosphate replacement and active vitamin D was observed in the change in 6MWT distance (improvement in walking distance of 43.2 metres), the extent of which cannot be conclusively assessed.

There was no statistically significant difference in the percentage of expected 6MWT distance between the treatment groups at week 64.

Anthropometric parameters: Height

The anthropometric parameter of height is assessed as a patient-relevant morbidity parameter, especially in children with characteristic, disease-related growth disorders. Data adjusted for age and sex (z scores) are preferred over absolute values.

In the UX023-CL301 study, patients' height was assessed by the change in standing height/ lying length as a z score and as a percentile (standing height/ lying length, sitting height) at week 64. In the UX023-CL301 study, growth was recorded as the change in standing height for patients ≥ 2 years, whereas lying length was collected for children < 2 years or for children who were unable to stand for the measurement.

The z scores of the reference population are based on a sample of healthy children from the USA. Country-specific z scores were not taken into account. Specific growth charts for children with XLH were not provided by the pharmaceutical company.

For the endpoint of absolute change in z score of standing height/ lying length, a statistically significant advantage of burosumab over phosphate replacement and active vitamin D was shown in the UX023-CL301 study, the clinical significance of which is unclear due to the magnitude of the difference shown.

Pain, physical functioning and fatigue using the Patient-Reported Outcomes Measurement Information System (PROMIS)

In the UX023-CL301 study, the PROMIS questionnaire was used to assess pain, physical functioning and fatigue in patients ≥ 5 years. For children aged 5 to 7 years, a version of the questionnaire was used that was filled out by the parents or guardians (external assessment). Children 8 years and older were given a version that was completed by the children themselves (self-assessment).

PROMIS is a system consisting of domain-specific tools (as item banks) for assessing patients' well-being.

For the endpoint of pain, physical functioning and fatigue assessed by PROMIS, no statistically significant difference was found between the treatment groups for the domains of pain impairment, physical functioning and fatigue in the UX023-CL301 study.

Pain intensity by means of Faces Pain Scale-Revised (FPS-R)

Pain intensity was assessed in the UX023-CL301 study for children ≥ 5 years using the FPS-R. The Faces Pain Scale - Revised (FPS-R) is a self-reported scale for assessing the intensity of acute pain in children. The FPS-R represents pain intensity graphically on a 6-point scale.

For the endpoint of pain intensity, no statistically significant difference was detected between the treatment arms.

Dental events

For the endpoint of dental events, no statistically significant difference was found between the treatment arms.

Quality of life

The quality of life of the paediatric patients was assessed in the UX023-CL301 study using the Short Form Health Survey-10 for children (SF-10). The SF-10 with 10 items was developed from the Child Health Questionnaire-PF50, comprising a total of 50 items. The SF-10 is a questionnaire completed by parents to assess the physical and psychosocial quality of life in healthy and sick children.
This questionnaire cannot be considered for the present benefit assessment due to a lack of information on various test quality criteria with regard to its validity.

Side effects

Serious adverse events (SAEs), severe AEs

In the UX023-CL301 study, there was no statistically significant difference between burosumab and the control arm for the endpoints of SAEs and severe adverse events (CTCAE grades 3 and 4).

Discontinuation due to AEs

For the endpoint of discontinuation due to AEs, no statistically significant difference was found between the treatment groups.

Specific AEs

For the endpoints of general disorders and administration site conditions, injury, poisoning and procedural complications, as well as respiratory, thoracic and mediastinal disorders (each SOC, AEs) and constipation (PT, AEs), there was a statistically significant difference to the disadvantage of burosumab compared to phosphate replacement and active vitamin D in each case.

For adolescents aged 13-17 years, no data were provided by the pharmaceutical company. The UX023-CL301 study enrolled only children with XLH aged 1-12 years.
The 2018 European Medicines Agency (EMA) assessment report[2] states that the RCT UX023-CL301 and the single-arm UX023-CL201 and UX023-CL205 studies were used as the basis for extrapolating efficacy and safety data from children aged 1-12 years to adolescents aged 13-17 years who are in the skeletal growth phase. The EMA assessment report of 2020[3] also extrapolates safety data from children aged 1-12 years and adults to adolescents with closed growth plates based on the UX023-CL301 and UX023-CL303 studies in the course of the extension of the therapeutic indication to adults and children and adolescents with closed growth plates. As the clinical manifestation of XLH differs between subjects with open growth plates and subjects with closed growth plates, the EMA does not extrapolate efficacy data from children to adolescents with closed growth plates.
XLH is a hereditary, progressive, chronic metabolic bone disease. Considering the fact that there is an identical underlying genetic cause of the disease, that the patients with open growth plates have a comparable pathophysiology, and considering the identical appropriate comparator therapy (phosphate replacement + active vitamin D in combination), it is assumed that there is a comparable therapeutic situation for adolescents with open growth plates compared to the 1-12 year old children. Even though no reliable data are available on the percentage of adolescents with open or closed growth plates, the additional benefit is derived for the total population.

<u>Overall assessment</u>

[2] Assessment report Crysvita EMA/148319/2018

[3] Assessment report Crysvita, EMA/423776/2020

[4] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

For the benefit assessment of burosumab for the treatment of X-linked hypophosphataemia (XLH) in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease, the pivotal, multicentre, randomised, open-label phase III UX023-CL301 study with a data cut-off at week 64 was used. Children aged 1-12 years were enrolled in this UX023-CL301 study and results on mortality, morbidity as well as side effects are shown.

There were no deaths in the UX023-CL301 study.

A statistically significant advantage of burosumab compared to placebo could be determined for the endpoint of the category morbidity walking ability measured by means of 6MWT, the extent of which cannot be conclusively assessed. For the endpoint of height (z score), there was a statistically significant advantage of burosumab over phosphate replacement and active vitamin D, the clinical significance of which is unclear due to the magnitude of the difference shown.

For the endpoints of percentage of expected 6MWT distance, pain, physical functioning and fatigue assessed by PROMIS and pain intensity assessed by FPS-R,

there were no statistically significant differences between the treatment groups.

No usable quality of life data were presented in the UX023-CL301 study.

In the overall assessment, there are no relevant advantages or disadvantages for burosumab in the side effects category.

For 13-17-year-old adolescents, no data were presented by the pharmaceutical company.

Considering the fact that there is an identical underlying genetic cause of the disease and a pathophysiology comparable to 1-12-year-old children is present for the 13-17-year-old adolescents with open growth plates, the additional benefit is derived for the overall population. The magnitude of the benefit shown in the endpoint 6MWT cannot be quantified. In the overall assessment, a non-quantifiable additional benefit is derived for children and adolescents aged 1 to ≤ 17 years with XLH with radiographic evidence of bone disease.

Reliability of data (probability of additional benefit)

There is a high risk of bias at study level for the UX023-CL301 study presented due to the open-label study design.

In the UX023-CL301 study, burosumab was compared to phosphate replacement and active vitamin D in children aged 1 to 12 years with XLH.

The marketing authorisation population of 13 to 17-year-olds is not enrolled in the presented UX023-CL301 study. It remains unclear whether the results from the UX023-CL301 study are also applicable to XLH patients aged 13-17 years with closed growth plates.

In the UX023-CL301 study, a dose increase of burosumab was only possible up to a maximum of 1.2 mg/kg body weight and not 2 mg/kg body weight as stated in the product information. The extent to which this affects the effects on patient-relevant endpoints observed in the UX023-CL301 study remains unclear.

Furthermore, there are differences in the 6MWT distance to baseline between the study arms. While children in the burosumab arm walked 366 m at baseline (corresponding to about 62% of the expected walking distance), children in the control group walked 451 m at baseline (corresponding to about 76% of the expected walking distance). Although this variable was taken into account as a covariate in the model, it is unclear to what extent the difference can be compensated for by this adjustment. The observed benefit for burosumab at the 6MWT distance at week 64 is therefore subject to uncertainty.

In the overall assessment, this results in a hint for a non-quantifiable additional benefit concerning the significance of the evidence.

2.1.4 Summary of the assessment

The present assessment is a new benefit assessment of the active ingredient burosumab due to the exceeding of the €50 million turnover limit. Crysvita was approved under "special conditions" as an orphan drug.

The present assessment relates to the therapeutic indication "for the treatment of X-linked hypophosphataemia, in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease".

The G-BA determined phosphate replacement and active vitamin D (calcitriol or alfacalcidol) in combination to be the appropriate comparator therapy.
The benefit assessment of burosumab was based on the pivotal, multicentre, randomised, open-label phase III UX023-CL301 study with a data cut-off at week 64.

There were no deaths in the UX023-CL301 study.

A statistically significant advantage of burosumab compared to placebo could be determined for the endpoint of the category morbidity walking ability measured by means of 6MWT, the extent of which cannot be conclusively assessed. For the endpoint of height (z score), there was a statistically significant advantage of burosumab over phosphate replacement and active vitamin D, the clinical significance of which is unclear due to the magnitude of the difference shown.

For the endpoints of percentage of expected 6MWT distance, pain, physical functioning and fatigue assessed by PROMIS and pain intensity assessed by FPS-R, there were no statistically significant differences between the treatment groups.

No usable quality of life data were presented in the UX023-CL301 study.

In the overall assessment, there are no relevant advantages or disadvantages for burosumab in the side effects category.

Considering the fact that there is an identical underlying genetic cause of the disease and a pathophysiology comparable to 1-12-year-old children is present for the 13-17-year-old adolescents with open growth plates, the additional benefit is derived for the overall population. The magnitude of the benefit shown in the endpoint 6MWT cannot be quantified. In the overall assessment, a non-quantifiable additional benefit is derived for children and adolescents aged 1 to ≤ 17 years with XLH with radiographic evidence of bone disease.

Uncertainties remain due to the open-label study design, regarding the assessment of the endpoint 6MWT and the maximum permitted dose increase of burosumab, which is not in

accordance with the marketing authorisation. In addition, it remains unclear whether the results from the UX023-CL301 study are also applicable to XLH patients aged 13-17 years with closed growth plates.

In the overall assessment, for children and adolescents aged 1 to ≤ 17 years with XLH with radiographic evidence of bone disease, a hint for a non-quantifiable additional benefit over phosphate replacement and active vitamin D in combination is identified.

2.2 Number of patients or demarcation of patient groups eligible for treatment

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

The number of patients is the target population in statutory health insurance (SHI). The information is based on patient numbers based on the information provided by the pharmaceutical company in the dossier. The number of patients in the statutory health insurance target population specified there is, however, fraught with uncertainties. Within the enrolled patient group of 14 to under 18-year-olds, it was assumed that only a small percentage of them are in the skeletal growth phase. As a result, the specified range represents an underestimation of the number of patients.

2.3 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: 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.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 July 2022).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number

of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

For the cost representation only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

For dosages depending on body weight (BW), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were used as a [4]basis. The average body weight of children aged 1 year (11.6 kg) and of those aged 17 to < 18 years (67 kg) was used to calculate the range of annual treatment costs. The burosumab lower dose range limit of 9.28 mg is derived from the recommended starting dose of 0.8 mg/kg and the average body weight of children aged 1 year (11.6 kg); the upper limit corresponds to the maximum dose of 90 mg. Each dose is to be measured out exactly to the nearest 10 mg according to the product information.

According to the most recent guideline for the treatment of hereditary hypophosphataemic rickets, 20 - 40 mg of elemental phosphate per kg body weight (bw) should be administered in at least 5 individual doses.[5] Medicinal products for phosphate replacement in the form of infusion solution appear unsuitable for children and adolescents aged 1 to 17 years when used 5 times a day. The remaining medicinal product is dispensed as a coated tablet containing 602 mg of active ingredient. The recommended upper limit of 40 mg/kg BW can only be divided into 5 single doses per day (5 x 602 mg coated tablet) from the age of 18 years (BW: 77 kg). Consequently, the costs of phosphate replacement in children and adolescents aged below 17 years are not quantifiable in the presentation.

According to the guideline for the treatment of hereditary hypophosphataemic rickets, 20-30 ng calcitriol per kg BW or 50 ng alfacalcidol per kg BW, divided into 1-2 single doses, should be administered[5].

For the dose ranges of phosphate and vitamin D supplementation, the lower dosage recommendations are shown for the youngest age group and the highest dosage recommendations for the oldest age group.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Burosumab	continuously, every 14 days	26.1	1	26.1

[4] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

[5] DGKED e.V. S1 guideline 174-008: Hereditary hypophosphataemic rickets; last revised: 03.2016; https://www.awmf.org/uploads/tx_szleitlinien/174-008l_S1_Hereditaere_hypophosphataemische_Rachitiden_2016-05-abgelaufen.pdf

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Appropriate comparator therapy				
Phosphate replacement and active vitamin D (calcitriol or alfacalcidol) in combination				
Phosphate	continuously, 5 x daily	365	1	365
Active vitamin D				
Calcitriol	continuously, 1-2 x daily	365	1	365
or				
Alfacalcidol	continuously, 1-2 x daily	365	1	365

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Burosumab	0.8 mg/kg BW = 9.28 mg - 90 mg	10 mg - 90 mg	1 x 10 mg 3 x 30 mg	26.1 26.1	26.1 x 10 mg 78.3 x 30 mg
Appropriate comparator therapy					
Phosphate replacement and active vitamin D (calcitriol or alfacalcidol) in combination					
Phosphate 1-year-olds 17-year-olds	 20 mg/kg BW = 232 mg - 40 mg/kg BW = 2,680 mg	 232 mg 2680 mg	 incalculable incalculable	 365 365	 incalculable incalculable
Active vitamin D					
Calcitriol 1-year-olds 17-year-olds	 20 ng/kg BW = 232 ng - 30 ng/kg BW = 2,010 ng	 0.25 µg - 2 µg	 1 x 0.25 µg 4 x 0.5 µg	 365 365	 365 x 0.25 µg - 1,460 x 0.5 µg
or					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Alfacalcidol					
1-year-olds	50 ng/kg BW = 580 ng -	0.5 µg -	1 x 0.5 µg	365	365 x 0.5 µg -
17-year-olds	50 ng/kg BW = 3,350 ng	3.5 µg	3 x 1 µg + 1 x 0.5 µg	365	1,095 x 1 µg + 365 x 0.5 µg

Costs:

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Burosumab 10 mg	1 SFI	€ 2,842.90	€ 1.77	€ 161.76	€ 2,679.37
Burosumab 30 mg	1 SFI	€ 8,507.83	€ 1.77	€ 485.29	€ 8,020.77
Appropriate comparator therapy					
Phosphate 602 mg	100 CTA	€ 23.98	€ 1.77	€ 0.86	€ 21.35
Calcitriol 0.25 µg[6]	100 SC	€ 45.18	€ 1.77	€ 2.68	€ 40.73
Calcitriol 0.5 µg[6]	100 SC	€ 77.66	€ 1.77	€ 5.25	€ 70.64
Alfacalcidol 0.5 µg[6]	100 SC	€ 57.72	€ 1.77	€ 3.67	€ 52.28
Alfacalcidol 1 µg[6]	100 SC	€ 96.81	€ 1.77	€ 6.76	€ 88.28
Abbreviations: SFI = solution for injection, CTA = coated tablets, SC = soft capsules					

LAUER-TAXE® last revised: 1 July 2022

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the

[6] Fixed reimbursement rate

prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131, paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 10 March 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 31 January 2022 the pharmaceutical company submitted a dossier for the benefit assessment of burosumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 6 VerfO.

By letter dated 1 February 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient burosumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 April 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 2 May 2022. The deadline for submitting written statements was 23 May 2022.

The oral hearing was held on 7 June 2022.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated

by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 12 July 2022, and the proposed resolution was approved.

At its session on 21 July 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	10 March 2020	Determination of the appropriate comparator therapy
Working group Section 35a	31 May 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	7 June 2022	Conduct of the oral hearing
Working group Section 35a	14.06.2022; 06.07.2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	12 July 2022	Concluding discussion of the draft resolution
Plenum	21 July 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 21 July 2022

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

Prof. Hecken