Justification

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

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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.

For medicinal products for the treatment of a rare disease (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a paragraph 1, sentence 11,1 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. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half SGB V). Section 35a, paragraph 1, sentence 11,1st half SGB V thus guarantees an additional benefit for an approved orphan drug, although an evaluation of the orphan drug in accordance with the principles laid down in Section 35a paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds €50 million in the last 12 calendar months. According to Section 35a paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, subsection 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a paragraph 1 sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the authorisation studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the legal limit of €50 million and is therefore subject to an unrestricted benefit assessment (cf. Section 35a paragraph 1, sentence 12 SGB V). According to Section 35a paragraph 2 SGB V, the assessment by the G-BA 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

The active ingredient burosumab (burosumab) was listed for the first time on 15 April 2018 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 30 September 2020, burosumab received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2a letter a to Regulation (EC) No. 1234/2008 of the commission of 24 November 2008 concerning the examination of amendments to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

Burosumab for the treatment of x-linked hypophosphataemia (XLH) is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999.

In accordance with section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V), the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the authorisation studies by the G-BA.

On 24 October 2020, ie at the latest within four weeks after the disclosure, the pharmaceutical company on the approval of a new area of application, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient burosumab with the new therapeutic indication (x-linked hypophosphataemia, ≥ 18 years).

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 1 February 2021 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA made its decision on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G20-27) and the statements made in the written statements and oral hearing process, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for the marketing authorisation with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1, numbers 1 – 4 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:

1 General Methods, version 6.0 from 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1 Additional benefit of the medicinal product

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 (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.

2.1.2 Extent of the additional benefit and the significance of the evidence

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

Adult patients with X-linked hypophosphataemia (XLH)

Hint for a minor additional benefit.

Justification:

For the assessment of the additional benefit of burosumab for adults with X-linked hypophosphatemia, the pharmaceutical company presented the approval-based, multicenter, randomised, double-blind, placebo-controlled phase III study UX023-CL303 with data cut-off at week 24. In the UX023- CL303 study, a total of 134 patients were randomised in a 1: 1 ratio to the intervention arm (burosumab; N = 68) or the comparator arm (placebo; N = 66).

The patient population included in the UX023-CL303 study comprised adult patients aged 18 to 65 years with a confirmed diagnosis of XLH based on the typical clinical features of XLH in adults (e.g. short stature, bent legs) and at least one of the following features: documented PHEX mutation and / or iFGF23 level in serum> 30 pg / ml according to Kainos assay Another inclusion criterion was a reduced serum phosphate level (<2.5 mg / dL). The adult patients with XLH years included in the UX023-CL303 study had to show symptomatology in the form of bone pain.

The final criterion was the oral intake of phosphate and active vitamin D within 14 days before the second screening visit. The patients in the comparator arm of UX023-CL303 study were offered no conventional therapy with oral phosphate and active vitamin D, this, however, has no consequences, taking into account the procedural rules in the benefit assessment of orphan drugs.

Treatment with burosumab was carried out in UX023-CL303 study according to the product information at a dose of 1.0 mg / kg every 4 weeks.

The UX023-CL303 study is divided into a screening and a 24 week treatment period. This was followed by a one-armed continuation phase (weeks 25 to 48) and a one-armed, open extension phase (weeks 49 to 96).

Primary endpoint in the UX023-CL303 study reaching the mean serum phosphate level is above the lower limit of normal in the centre of the dose cycle In UX023-CL303 study more endpoints were collected in category mortality, morbidity and side effects.

The study originally stratified for "Worst pain in the last 7 days" (BPI-SF item 3). Stratification for Item 5 of the BPI-SF was incorrectly carried out. Since the recruitment had already started when the error was noticed, the stratified randomisation was continued with item 5. It is assumed that the study arms are comparable despite the error in the stratified randomisation and that the blinding could be maintained for the majority of the study population.

Mortality

There were no deaths in the UX023-CL303 study

Morbidity

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.

The serum phosphate level in UX023-CL303 study was raised at baseline, week 2, week 4, week 6, week 10, week 12, week 14, week 18, week 20, week 21, week 22, week 24 and at early discontinuation / end of treatment. In the UX023- CL303 study, the proportions in the treatment groups that had a mean serum phosphate value above the lower limit of the normal range in the middle (primary endpoint) and at the end of a dose cycle were evaluated.

For the endpoint proportion of patients with moderate serum phosphate levels ≥ 2.5 mg / dL in the middle of the dose cycle study CL303 UX023 demonstrated a statistically significant advantage of burosumab compared to placebo.

Evaluation at the end of the dosage cycle took place exclusively descriptive. At the end of the dose cycle, 46 patients from the burosumab arm (67.6%) and 4 subjects from the placebo arm (6.1%) achieved a mean serum phosphate level of ≥ 2.5 mg / dL.

The results of the serum phosphate level show that in the majority of patients 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.

Walking ability: 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).

In the written statement procedure, the pharmaceutical company plausibly demonstrated that, due to a calculation error, an incorrect baseline value was corrected after the database was closed in the double-blind phase of the UX023-CL303 study. The corrected analysis of the pharmaceutical company from the dossier is therefore used for the benefit assessment.

In UX023-CL303 study, a statistically significant advantage of burosumab over placebo was found in the mean change in the 6MWT distance at week 24 compared to baseline (LS mean difference: 19.8 meters), the extent of which cannot be judged conclusively.

Stiffness, Physical Function, Pain: Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Questionnaire

The WOMAC was used in the UX023-CL303 study for the patient-reported assessment of pain, stiffness and physical function.

For the "pain" subscale, there was no statistically significant difference between the treatment groups in the mean change from baseline to week 24.

For the WOMAC questionnaire, the pharmaceutical company submitted post hoc responder analysis in the opinion process on the proportion of patients who showed a decrease of at least 15 normalised units (nu) after 24 weeks.

For the "stiffness" subscale the responder analysis (decrease by ≥ 15 nu) showed a statistically significant advantage of burosumab over placebo. For the subscale "physical function", no statistically significant difference between the treatment groups could be found in the

responder analysis. No responder analysis were subsequently submitted for the "Pain" subscale

Pain: Brief Pain Inventory - Short Form (BPI-SF)

In the UX023- CL303 study, pain was recorded as a patient-reported endpoint using the BPI-SF questionnaire

For the domains of Pain Intensity and Pain Impairment of the BPI-SF, there was no statistically significant difference between the treatment groups in the mean change from baseline to week 24.

In the basis of item 3 "Worst pain", responder analysis were carried out for reductions of > 15 and> 30%. For the benefit assessment, the responder analysis is used for the reduction of> 15%

For the endpoint "worst pain", no statistically significant difference between the treatment groups could be found in the responder analysis of the BPI-SF for the reduction of> 15%.

Fatigue: Brief Fatigue Inventory (BFI)

Fatigue was recorded in the CL303 study using the BFI. For the endpoint Fatigue collected by BFI, UX023- CL303 study found in the mean change from baseline to week 24, no statistically significant difference between treatment groups.

Disease state: Patient Global Impression of Improvement (PGI-I)

The patient-reported assessment of the disease state was carried out in the UX023-CL303 study at baseline using the PGI-S and in the further course of the study using the PGI-I.

No statistically significant difference between burosumab and placebo was shown in the mean change from baseline to week 24 for the endpoint "State of disease recorded using PGI-I".

Quality of life

Quality of life was not recorded in the UX023-CL303 study.

Side effects

In the UX023 CL- 303 study 2 patients of the burosumab arm (2.9%) and 2 patients in the control arm (3.0%) each had serious adverse events (SAEs). For 8 patients in the burosumab arm (11.8%) and 9 patients in the control arm (13.6%) showed each severe adverse events (AEs CTCAE grade 3 or 4). From this, no overall difference between the treatment groups can be derived for the endpoints SAEs and AEs CTCAE grade 3 or 4.

In the UX023-CL303 study no patient discontinued the therapy with burosumab or placebo due to AEs. There is no difference between the treatment groups.

At the level of the SOC (system organ class) and PT (preferred term), it cannot be ruled out that symptomatology of XLH are also included. A statistically significant difference in favour of burosumab was shown for the endpoints arthralgia (PT) and oropharyngeal pain (PT).

Overall, there are no advantages or disadvantages for burosumab in the side effects category.

Overall assessment / conclusion

For the benefit assessment of burosumab for adults with X-linked hypophosphatemia, the pharmaceutical company presented the approval-based, multicenter, randomised, double-blind, placebo-controlled phase III study UX023-CL303 with data cut-off at week 24.

The UX023-CL303 study produced results on mortality, morbidity and side effects.

There were no deaths in the UX023-CL303 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 clinically important endpoint serum phosphate value, study UX023-CL303 showed a statistically significant advantage of burosumab over placebo for the proportion of subjects with mean serum phosphate levels ≥ 2.5 mg / dL in the middle of the dose cycle At the end of the dose cycle, 46 patients from the burosumab arm (67.6%) and 4 subjects from the placebo arm (6.1%) achieved a mean serum phosphate level of ≥ 2.5 mg / dL. The results show that in the majority of patients the Serum phosphate levels during treatment with burosumab reaches the normal range.

There were no statistically significant differences between the treatment groups for the endpoints Pain, recorded using WOMAC, Fatigue, recorded using BFI, and Disease status, recorded using PGI-I.

For the "stiffness" subscale the responder analysis (decrease by ≥ 15 nu) showed a statistically significant advantage of burosumab over placebo. For the subscale "physical function", no statistically significant difference between the treatment groups could be found in the responder analysis. No responder analysis were subsequently submitted for the "Pain" subscale

For the domains of Pain Intensity and Pain Impairment of the BPI-SF, there was no statistically significant difference between the treatment groups in the mean change from baseline to week 24. For the endpoint "Worst pain", no statistically significant difference between the treatment groups could be found in the responder analysis of the BPI-SF (item 3) for the reduction of > 15%.

Quality of life was not recorded in the UX023-CL303 study.

Overall, there are no advantages or disadvantages for burosumab in the side effects category.

Overall, the G-BA comes to the conclusion that there is minor additional benefit of burosumab for the treatment of adult patients with XLH.

Significance of the evidence

For the benefit assessment of burosumab for the treatment of adult patients with XLH, the 24 week, multicenter, randomised, double-blind placebo-controlled phase III study UX023-CL303 was presented. The UX023-CL303 study presented had a low risk of bias at study level.

In the UX023-CL303 study, burosumab was compared with placebo in adult XLH patients who exhibited symptomatology in the form of bone pain. The approved population does not contain any restriction with regard to symptomatology. It remains unclear whether the results of the UX023-CL303 study can also be applied to patients who have no symptomatology in the form of bone pain.

Due to the chronic course of XLH and the necessary long-term treatment of the patients, the 24 week treatment duration of the presented RCT for assessing the sustainability of the effects is fraught with uncertainties.

Overall, the results for the endpoints in the side effects category are subject to uncertainty, as there was a high number of deviations in the study documents (study reports, recalculation

document). Results-driven reporting cannot be assumed, however, as adjustments were made during the double-blind study phase.

For the subscales "stiffness" and "physical function" of the WOMAC, post hoc responder analysis were submitted by the pharmaceutical company. The information provided by the pharmaceutical company does not clearly show how the non-adjusted RR including 95% CI and p-values were calculated. For the adjusted RR, the rationale for choosing the adjustment factors is unclear. In addition to the treatment group, the pharmaceutical company specified the factors "Brief Pain Inventory (BPI) Average pain and age" as independent variables, but the stratified randomisation was based on BPI-SF Item 5 (average pain) and region. It is unclear whether a statistically significant difference between the treatment arms would have been determined for the "stiffness" subscale of the WOMAC, even with adequate consideration of the stratification factors of the randomisation.

In the overall review the result is a hint for minor additional benefit with regard to significance of the evidence.

2.1.3 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient burosumab (CRYSVITA®). Burosumab was approved as an orphan drug under "special conditions".

The therapeutic indication assessed here is as follows: "Burosumab is used to treat adult patients with X-linked hypophosphataemia (XLH)".

For the benefit assessment of burosumab for adults with XLH, the pharmaceutical company presented the approval-based, multicenter, randomised, double-blind, placebo-controlled phase III study UX023-CL303 with data cut-off at week 24. The UX023-CL303 study produced results on mortality, morbidity and side effects.

There were no deaths in the UX023-CL303 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 clinically important endpoint serum phosphate value, study UX023-CL303 showed a statistically significant advantage of burosumab over placebo for the proportion of subjects with mean serum phosphate levels ≥ 2.5 mg / dL in the middle of the dose cycle. At the end of the dose cycle, 46 patients from the burosumab arm (67.6%) and 4 subjects from the placebo arm (6.1%) achieved a mean serum phosphate level of ≥ 2.5 mg / dL. The results show that in the majority of patients the Serum phosphate levels during treatment with burosumab reaches the normal range.

There were no statistically significant differences between the treatment groups for the endpoints Pain, recorded using WOMAC, Fatigue, recorded using BFI, and Disease status, recorded using PGI-I.

For the "stiffness" subscale the responder analysis (decrease by ≥ 15 nu) showed a statistically significant advantage of burosumab over placebo. For the subscale "physical function", no statistically significant difference between the treatment groups could be found in the responder analysis. No responder analysis were subsequently submitted for the "Pain" subscale

For the domains of Pain Intensity and Pain Impairment of the BPI-SF, there was no statistically significant difference between the treatment groups in the mean change from baseline to week 24. For the endpoint "Worst pain", no statistically significant difference between the treatment groups could be found in the responder analysis of the BPI-SF (item 3) for the reduction of > 15%.

Quality of life was not recorded in the UX023-CL303 study.

Overall, there are no advantages or disadvantages for burosumab in the side effects category.

Uncertainties with regard to the significance of the evidence arise due to the 24 week treatment duration for assessing the sustainability of the effects, with regard to the adjustment and stratification factors of the randomisation for the responder analyses of the WOMAC and as a result of deviations in the study documents on endpoints in the side effects category. It remains unclear whether the results of the UX023-CL303 study can also be applied to patients who have no symptomatology in the form of bone pain.
Overall, the G-BA comes to the conclusion that there is a hint for a minor additional benefit of burosumab for the treatment of adult patients with XLH.

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

Adult patients with X-linked hypophosphataemia (XLH)

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 by the pharmaceutical company is, however, fraught with uncertainties. In the source on prevalence used by the pharmaceutical company,[2] reference is made to a possible underestimation. In addition, a routine data analysis was identified for Germany that shows a higher number of adults with XLH. As a result, the specified range represents an underestimation of the number of patients.

The restriction made by the pharmaceutical company to patients who do not respond to phosphate substitution within one year is not followed, as this restriction does not result from the present therapeutic indication.

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: 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.

[2] Hawley S, Shaw NJ, Delmestri A, et al. Prevalence and Mortality of Individuals With X-Linked Hypophosphatemia: A United Kingdom Real-World Data Analysis. J Clin Endocrinol Metab 2020; 105(3): e871-e878.

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: 15 March 2021).
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 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 [3]basis The average body weight of an adult was used as the basis for calculating the range of annual treatment costs The lower limit of the dose range of 80 mg results from the recommended starting dose of 1.0 mg / kg and the average body weight of adults (77 kg) and the requirements of the burosumab product information to round up or down to the nearest 10 mg. The upper limit corresponds to the maximum dose of 90 mg.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Burosumab	Continuously, every 28 days	13.0	1	13.0

Consumption:

Designation of the therapy	Dosage/ application	Dosage/patient/days of treatment	Consumption according to potency/day of treatment	Days of treatment/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Burosumab	1Mg/kg KG = 77 mg - 90 mg	80 mg – 90 mg	2 x 30 mg + 1 x 20 mg - 3 x 30 mg	13.0	26 x 30 mg + 13 x 20 mg - 39 x 30 mg

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

Costs:
In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal product:

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 20 mg	1 ILO	€ 6,261.26	€ 0.00	€ 1.77	€ 6,259.49
Burosumab 30 mg	1 ILO	€ 9,386.79	€ 0.00	€ 1.77	€ 9,385.02
Abbreviations: ILO = solution for injection					

LAUER-TAXE® last revised: 15 March 2021

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 or patient information leaflet, the differences 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.

For the cost representation no additionally required SHI services are considered.

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 1.10.2009 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 special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) all surcharges for the production of parenteral preparations containing cytostatic drugs a maximum 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 special agreement on contractual unit costs of retail pharmacist services (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 sales 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 special agreement on contractual unit costs retail pharmacist services (Hilfstaxe).

3. Bureaucratic costs

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

On 24 October 2020 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 2 VerfO.

The benefit assessment of the G-BA was published on 1 February 2021 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting the written statements was 22 February 2021.

The oral hearing was held on 9 March 2021.

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 were discussed at the session of the subcommittee on 7 April 2021, and the draft resolution was approved.

At its session on 15 April 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	26 January 2021	Information of the benefit assessment of the G-BA
Working group Section 35a	03 March 2021	Information on written statement procedures received; preparation of the oral hearing
Subcommittee Medicinal products	09 March 2021	Conduct of the oral hearing, Commissioning of the G-BA with the supplementary assessment of documents

Working group Section 35a	17 March 2021 31 March 2021	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal products	7 April 2021	Concluding consultation of the draft resolution
Plenum	15 April 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 April 2021

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

Prof. Hecken