Justification

Gemeinsamer Bundesausschuss

to 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 (Reassessment after the Deadline: Hypophosphataemia)

of 2 April 2020

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.

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 of the Council of 16 December 1999, the additional medical benefit is deemed to be proven by the marketing authorisation according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy need not be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, numbers 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 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 during the last twelve 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, paragraphs 1–6 VerfO, in particular regarding the additional medicinal 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). On the basis of the statutory requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is deemed to have been proven through the grant of 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, in the case of 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 provided is assessed exclusively on the basis of the approval 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 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 in such a way 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 of 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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The pharmaceutical company first submitted a dossier for the early benefit assessment of the active ingredient burosumab (Crysvita®) on 12 April 2018. The resolution of 4 October 2018 passed by the G-BA in these proceedings was limited until 1 October 2019. In accordance with Section 4, paragraph 3, No. 5 AM-NutzenV in conjunction with Chapter 5, Section 8, paragraph 1, No. 5 VerfO, the benefit assessment procedure for the medicinal product (Crysvita®) shall start again on the day the deadline has expired.

For this purpose, on 26 September 2019, the pharmaceutical company submitted the dossier on the benefit assessment to the G-BA in due time (Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, No. 5 VerfO).

Crysvita® for the treatment of hypophosphotasia 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 sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The probability and extent of the additional benefit are assessed on the basis of the pivotal study(s) by the G-BA.

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 2 January 2020 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 has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G19-15) 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 studies relevant for 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 through 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 arrived at the following assessment:

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 with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons.

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

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

1 General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

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

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

Justification:

For the assessment of the additional benefit of burosumab for children 1 year of age and older and adolescents with growing skeletons with X-linked hypophosphataemia with radiographic evidence of bone disease, the pharmaceutical company presented the pivotal, multi-centre, randomised, open-label Phase III Study UX023-CL301 with a data cut-off at week 64. The approval population of 13–17 year olds is not included in Study UX023-CL301.

In Study UX023-CL301, burosumab was compared with conventional therapy (consisting of oral phosphate and active vitamin D) in children aged 1 to 12 years with XLH. The patient population included in Study UX023-CL301 included paediatric XLH patients (1–12 years) with evidence of a PHEX mutation. Patients with radiological evidence of rickets (RSS overall score ≥ 2.0) as well as reduced serum phosphate levels, serum creatinine below the age-adjusted upper normal range, and serum 25(OH)D above the lower normal value were enrolled in Study UX023-CL301. Another enrolment criterion was the oral intake of phosphate and active vitamin D before randomisation. In addition, a standing height of < 50th percentile was determined.

“Rickets symptomatology by means of Radiographic Global Impression of Change (RGI-C)” was collected as the primary endpoint of Study UX023-CL301. The randomisation of patients was stratified according to severity of rickets (RSS ≤ 2.5 vs > 2.5), age (< 5 vs ≥ 5 years), and region.

A total of 61 patients were randomised at a ratio of 1:1 to the burosumab arm (N = 29) or the conventional therapy arm (N = 32). Patients in the intervention group received burosumab at the 2-week dosage in compliance with the marketing authorisation, whereby simultaneous treatment with conventional therapy was contraindicated. In the control group, all patients received the conventional therapy, which was dosed individually. In addition to the primary endpoint, Study UX023-CL301 investigated endpoints in the mortality, morbidity, quality of life, and side effects categories. In the course of Study UX023-CL301, protocol changes and amendments (e.g. introduction of a single-arm extension phase, specification of the enrolment and disqualification criteria, change of the PROMIS version from 1.0 to 2.0) were made.

Mortality

No deaths occurred in the UX023-CL301 study.

Morbidity

Rickets symptomatology by means of Radiographic Global Impression of Change (RGI-C)

In Study UX023-CL301, the RGI-C score was used as the primary endpoint to measure bone mineralisation. The RGI-C rating scale evaluates changes in XLH-associated rickets over time by means of X-ray imaging on a scale from -3 to +3. A score of −3 indicates a severe deterioration of XLH-associated rickets, while +3 indicates an almost complete or complete recovery of XLH-associated rickets in comparison with baseline.

For the radiological endpoint RGI-C, there was a statistically significant change at week 64 in favour of burosumab compared with conventional therapy.

There are no data available to prove the validity of RGI-C as a surrogate for morbidity in the present therapeutic indication.

Rickets symptomatology by means of Rickets Severity Scale (RSS)

In Study UX023-CL301, rickets symptomatology was surveyed as a endpoint by means of Rickets Severity Scale (RSS) in order to assess the severity of rickets on an absolute scale of 0–10 using X-rays of the wrists and knees The RSS is important for both diagnosis and follow-up. A total RSS score of 10 indicates severe rickets, while a score of 0 indicates no rickets.

In Study UX023-CL301, for RSS, a statistically significant change at week 64 in favour of burosumab compared with the conventional therapy was shown. The evidence provided by the pharmaceutical company is not adequate to demonstrate a clear correlation or validation of the surrogate endpoint (Rickets symptomatology by means of RSS) with/for the patient-relevant endpoints (e.g. pain, mobility, walking ability, and mortality).

Serum phosphate

Increasing the pathologically decreased serum phosphate level until the normal range is achieved is the clinically significant parameter as a therapeutic goal.

In Study UX023-CL301, for the endpoint serum phosphate level, a statistically significant change at week 64 in favour of burosumab compared with conventional therapy was shown.

The results on serum phosphate levels indicate that serum phosphate levels under therapy with burosumab reach the normal range and that the pathologically altered serum phosphate level caused by the genetic defect is stabilised.

Anthropometric parameters: Height

The anthropometric parameter body height is estimated 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.

As part of Study UX023-CL301, the height of the patients was surveyed via the change in standing height/lying length as z-score and as percentiles (standing height/lying length, sitting height) at week 64. In Study UX023-CL301, growth was recorded as change in standing height in patients ≥ 2 years, whereas the lying length was recorded 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 US. No consideration was made for country-specific z-scores. Specific growth charts for children with XLH were not provided by the pharmaceutical company.

In Study UX023-CL301, for the endpoint absolute change in the z-score of standing height/lying length, a statistically significant advantage of burosumab compared with conventional therapy was shown; however the clinical significance of this is unclear because of the magnitude of the difference shown.

Motor function: 6 minute walk test (6MWT)

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

In Study UX023-CL301, walking ability was assessed using the 6MWT in children who were at least 5 years old at baseline. A modified approach contrary to the American Thoracic

Society statement was chosen. The measurement of the physical endurance of the patient or the coping with activities of daily life is basically a patient-relevant endpoint.

In Study UX023-CL301, a statistically significant advantage of burosumab compared with conventional therapy was found in the change in the 6MWT distance to week 64 (improvement of the walking distance by 43.2 meters); however, the extent of this cannot be conclusively assessed.

In the percentage of the expected 6MWT distance, there was no statistically significant difference between the treatment groups at week 64.

Pain, physical function and fatigue by means of the Patient-Reported Outcomes Measurement Information System (PROMIS)

In Study UX023-CL301, the PROMIS questionnaire was used to assess pain, physical function, and fatigue in patients ≥ 5 years.

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

In Study UX023-CL301, items were selected from the PROMIS item banks of the domains pain impairment, physical function, and fatigue (Version 2.0), and a static questionnaire version was generated for self- and third-party assessment. However, the items do not fully correspond to the items of the short forms proposed by the developers. A joint evaluation of the data from self-assessment (≥ 8 years) and external assessment (5–7 years) took place. The extent to which the joint evaluation of data from self and external assessments of the PROMIS methodology is possible is not clear from the descriptions and investigations of the instrument. There are also limitations with regard to change sensitivity.

For the endpoints pain, physical function, and fatigue surveyed by means of PROMIS, in Study UX023-CL301, no statistically significant difference was found between the treatment groups for the domains pain impairment, physical function, and fatigue in the T-score.

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

In Study UX023-CL301, pain intensity in patients ≥ 5 years was surveyed using 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 displays pain intensity graphically on a 6-point scale.

At low baseline values, no statistically significant difference between burosumab and conventional therapy was shown with regard to the change in acute pain intensity at week 64 as measured by FPS-R.

Quality of life

In Study UX023-CL301, the quality of life of paediatric patients was assessed using the Short Form Health Survey-10 for Children (SF-10). The SF-10 is a questionnaire completed by parents to assess the physical and psychosocial quality of life in healthy and sick children. Because of a lack of information on various test quality criteria, the validity of this questionnaire cannot be conclusively assessed at present.

Side effects

In Study UX023-CL301, for the endpoints serious adverse events (SAE) and severe adverse events (AE CTCAE grade 3 and 4), no statistically significant differences were shown between the burosumab arm and the control arm.

For the endpoint discontinuation because of AE, no statistically significant difference between burosumab and conventional therapy was shown.

The most common adverse events at the SOC level (with a cut-off at ≥ 10% incidence in one of the arms and a difference of at least 10% between the arms; to the detriment of burosumab) were in Study UX023-CL301: general disorders and administration site conditions, gastrointestinal disorders, respiratory, thoracic, and mediastinal disorders, musculoskeletal and connective tissue disorders, nervous system disorders, skin and subcutaneous tissue disorders, injury, poisoning, and procedural complications, ear and labyrinth disorders, investigations, and metabolism and nutrition disorders.

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

Overall assessment/conclusion

For the benefit assessment of burosumab for children 1 year of age and older and adolescents with growing skeletons with X-linked hypophosphataemia with radiographic evidence of bone disease, the pivotal, multi-centre, randomised, open-label Phase III Study UX023-CL301 with a data cut-off at week 64 is used. The UX023-CL301 study will provide results on mortality, morbidity, and side effects.

No deaths occurred in the UX023-CL301 study.

For the endpoint of the morbidity category motor function assessed by 6MWT, a statistically significant advantage of burosumab compared with conventional therapy (consisting of oral phosphate and active vitamin D) was found; however, the extent of this cannot be conclusively assessed. For the endpoint standing height/lying length (z-score), a statistically significant advantage of burosumab compared with conventional therapy was shown; however the clinical significance of this is unclear because of the magnitude of the difference shown.

For the clinically important endpoint serum phosphate, there was a statistically significant difference in favour of burosumab compared with conventional therapy. The results indicate that the serum phosphate level reaches the normal range under therapy with burosumab.

For the endpoint rickets symptomatology assessed by RGI-C and RSS, there was a statistically significant difference in favour of burosumab compared with conventional therapy. However, the surrogate validation for the two radiological endpoints RSS and RGI-C was not sufficiently proven for patient-relevant endpoints.

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

In the UX023-CL301 study, no usable data on quality of life were submitted.

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

In the overall view, there is a non-quantifiable additional benefit because the scientific data basis does not allow quantification.

Significance of the evidence

For Study UX023-CL301, there is risk of bias at the study level because of the open study design.

In Study UX023-CL301, burosumab was compared with conventional therapy in children aged 1 to 12 years with XLH. The approval population of 13–17 year olds is not included in

Study UX023-CL301. It remains unclear whether the results from the UX023-CL301 study are also applicable to XLH patients aged 13–17 years.

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, children in the control group walked 451 m at baseline. Although this variable was included as a covariate in the model, the extent to which the difference can be compensated for by this adjustment is unclear. There was also no adjustment for age to baseline for the 6MWT, although this was pre-specified. The advantage for burosumab in the 6MWT distance at week 64 is therefore subject to uncertainties.

Because of the different ways of surveying adverse events (by means of house rounds, telephone interviews) between the study arms, the results in the side effects category may be biased.

In the overall view, there is a hint for a non-quantifiable additional benefit in terms of the significance of the evidence.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the medicinal product Crysvita® with active ingredient burosumab after the deadline. Burosumab was approved as an orphan drug under “special conditions” and is indicated for the “treatment of children 1 year of age and older and adolescents with growing skeletons with X-linked hypophosphataemia with radiographic evidence of bone disease”.

The benefit assessment of burosumab was based on the pivotal, multi-centre, randomised, open-label Phase III study UX023-CL301 with a data cut-off at week 64. The UX023-CL301 study will provide results on mortality, morbidity, and side effects.

No deaths occurred in the UX023-CL301 study.

For the endpoint of the morbidity category motor function assessed by 6MWT, a statistically significant advantage of burosumab compared with conventional therapy (consisting of oral phosphate and active vitamin D) was found; however, the extent of this cannot be conclusively assessed. For the endpoint standing height/lying length (z-score), a statistically significant advantage of burosumab compared with conventional therapy was shown; however the clinical significance of this is unclear because of the magnitude of the difference shown.

For the clinically important endpoint serum phosphate, there was a statistically significant difference in favour of burosumab compared with conventional therapy. The results indicate that the serum phosphate level reaches the normal range under therapy with burosumab.

For the endpoint rickets symptomatology assessed by RGI-C and RSS, there was a statistically significant difference in favour of burosumab compared with conventional therapy. However, the surrogate validation for the two radiological endpoints RSS and RGI-C was not sufficiently proven for patient-relevant endpoints.

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

In the UX023-CL301 study, no usable data on quality of life were submitted.

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

In the overall view, there is a hint for a non-quantifiable additional benefit because the scientific data basis does not allow quantification.

2.2 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.

The number of patients is the target population in the statutory health insurance (SHI). The data are based on patient numbers, which, in turn, are based on the information provided by the pharmaceutical company in the dossier. However, the number of patients in the SHI target population stated there is subject to uncertainty. Within the patient group of 14 to under 18-year-olds, it was assumed that only a small proportion of these are in the skeletal growth phase. Consequently, the range given 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: 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.

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 2020).

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”, the 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”[2] were used as a basis: To calculate the range of annual treatment costs, the average body weight of children aged 1 year (11.6 kg) and 17 to < 18 years (67 kg) was used. The lower limit of the dose range of 9.28 mg results from the recommended initial 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. According to the product information, each dose should be calculated to the nearest 10 mg.

[2] German Federal Office For Statistics, Wiesbaden 2018: http://www.gbe-bund.de/

Treatment duration:

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

Usage and consumption:

Designation of the therapy	Dosage/application	Dose/patient/treatment day	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Burosumab	9.28 mg[3] – 90 mg	10 mg – 90 mg	1 × 10 mg – 3 × 30 mg	26.1	26.1 × 10 mg – 78.3 × 30 mg

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	Package 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	€ 3,135.72	€ 1.77	€ 0.00	€ 3,133.95
Burosumab 30 mg	1 SFI	€ 9,386.79	€ 1.77	€ 0.00	€ 9,385.02

[3] 0.8 mg/kg × 11.6 kg

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Abbreviations: SFI = solution for injection					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 March 2020

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 medical treatment or the prescription of other services when using the medicinal product to be assessed 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 standard expenditure in the course of the treatment are not shown.

No additionally required SHI services are taken into account for the cost representation.

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe; contract on price formation for substances and preparations of substances) 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 special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"] (last revised: 10. Supplementary Agreement to the Agreement on Pricing of Substances and Preparations of Substances of 1 March 2020), surcharges for the preparation of parenteral preparations containing cytostatics of a maximum of € 81 per ready-to-use preparation and for the preparation of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall apply. These additional costs are not added to the pharmacy sales price but rather follow the rules for calculating 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 ingredients, the invoicing of discards, and the calculation of application containers and carrier solutions according to the regulations of Annex 3 of the 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 26 September 2019, 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 5 VerfO.

The benefit assessment of the G-BA was published on 2 January 2020 together with the IQWiG assessment of treatment costs and patient numbers on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 23 January 2020.

The oral hearing was held on 10 February 2020.

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 24 March 2020, and the proposed resolution was approved.

On 2 April 2020, the G-BA resolved by written statement to amend the Pharmaceuticals Directive.

The patient representatives support the resolution.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	18 December 2019	Information of the benefit assessment of the G-BA
Working group Section 35a	4 February 2020	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal Products	10 February 2020	Conduct of the oral hearing
Working group Section 35a	18 February 2020 3 March 2020 17 March 2020	Consultation on the dossier evaluation 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	24 March 2020	Concluding discussion of the draft resolution
Plenum	2 April 2020	Written resolution on the amendment of Annex XII of the AM-RL

Berlin, 2 April 2020

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

Prof. Hecken