IQWiG Reports – Commission No. A22-12

Burosumab (X-linked hypophosphataemia, ≥ 18 years) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Burosumab (X-chromosomale Hypophosphatämie, ≥ 18 Jahre) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 25 April 2022). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Monika Helfert and Martha Kirchhoff.

IQWiG thanks the respondents for participating in the written exchange about how they experienced the disease and its treatment and about the treatment goals. The respondents were not involved in the actual preparation of the dossier assessment.

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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
XLH	X-linked hypophosphataemia

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug burosumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 1 February 2022.

Research question

The aim of this report is to assess the added benefit of burosumab in comparison with phosphate substitution as the appropriate comparator therapy (ACT) in adult patients with X-linked hypophosphataemia (XLH).

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of burosumab

Therapeutic indication	**ACT**[a]
Patients with XLH aged 18 years or older[b]	Phosphate substitution[c]
a. Presented is the ACT specified by the G-BA. b. In accordance with the G-BA, patients with the present therapeutic indication are presumed to be symptomatic and hence in need of treatment. c. In accordance with the G-BA, vitamin D substitution (calcitriol or alfacalcidol) is presumed to be in place. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; XLH: X-linked hypophosphataemia	

The company formulated a different research question. This is not appropriate, as discussed in the section below. The present benefit assessment was carried out using the ACT specified by the G-BA, phosphate substitution in conjunction with vitamin D substitution (calcitriol or alfacalcidol).

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

Deviating research question of the company

The company departed from the research question of the present benefit assessment by distinguishing 2 patient populations within adults with XLH:

1) Adults who respond to phosphate substitution within 1 year
2) Adults who do not respond to phosphate substitution within 1 year

In the company's view, a response is exhibited mainly by the achievement of a serum phosphate level in the lower normal range of ≥ 2.5 mg/dL. The company argues that improvement of clinical symptoms is another factor in the assessment of treatment response.

Overall, the company presumes that virtually all adults with XLH belong to the subpopulation which fails to respond to phosphate administration. Arguing that these patients are not indicated for further phosphate substitution due to potential side effects, the company defined best supportive care (BSC) as the ACT for the patient population it defined as population 2.

Having performed the analysis without the patient population who responded to phosphate substitution within 1 year, the company did not specify an ACT for this patient population.

Inappropriate approach chosen by the company

The company's approach is inadequate for multiple reasons. First, the evidence provided by the company does not substantiate the response criteria it used (serum phosphate level ≥ 2.5 mg/dL and various symptoms) nor the time limit of 1 year it applied to treatment response. Second, the evidence currently available in the therapeutic indication does not bear out the assumption that symptomatic patients who have not achieved improvement of clinical symptoms under phosphate substitution are generally no longer indicated for further phosphate substitution. No convincing argument in this regard was made by the company either.

To support its assumption that none of the patients in the present therapeutic indication respond to phosphate substitution, the company cites the study used for extending the indication for burosumab (UX023-CL303 RCT). The company argues that study participants had already received phosphate substitution at some point in their medical history, but still exhibited disease progression. On this basis, the company reasons that the patients failed to respond to phosphate substitution and extrapolates this conclusion to the total population of adults with XLH. The company concludes that, given the lack of response and potential side effects, phosphate substitution is unsuitable for these patients. However, deterioration under therapy is not proof of ineffectiveness. The company has not submitted any further evidence of benefit or harm of phosphate substitution in adults with XLH who failed to respond to phosphate substitution within 1 year.

Postulating the absence of treatment alternatives, the company defined BSC as the comparator therapy for the patient population not responding to phosphate substitution within 1 year. As discussed above, however, phosphate substitution is indicated for all symptomatic adults with XLH.

The company's reasoning was therefore rejected. The present benefit assessment has been carried out for the entire target population without breaking down the patient population.

Results

The check for completeness of the study pool revealed no relevant studies comparing burosumab versus the ACT of phosphate substitution.

For its divergent research question, the company used in its assessment the UX023-CL303 RCT comparing burosumab with placebo. The company's approach is not appropriate. The UX023-CL303 RCT is unsuitable for assessing the benefit of burosumab versus the ACT.

Evidence provided by the company

The company submitted the randomized, double-blind, multicentre UX023-CL303 study comparing burosumab with placebo in adults with XLH. This study included a total of 134 patients with XLH aged 18 to 65 years. Other inclusion criteria were a serum phosphate level < 2.5 mg/dL and the existence of skeletal pain. The study excluded patients who had taken phosphate or vitamin D metabolites as well as patients with elevated serum calcium concentrations or an elevated serum concentration of intact parathyroid hormone.

Allocation to the study arms of burosumab (N = 68) and placebo (N = 66) was randomized and stratified by pain intensity and region. The controlled treatment phase (burosumab versus placebo) had a duration of 24 weeks. Afterwards, patients switched from the comparator arm into the burosumab arm, in which treatment was continued until Week 96. At the US study sites, treatment continuation was allowed, at most until Week 149.

Burosumab or placebo was administered subcutaneously every 4 weeks. Allowed comedications included, in particular, pain medicines at unchanged dosages and treatment regimens. The study disallowed the administration of phosphate or active vitamin D (e.g. calcitriol) for the treatment of XLH, and any existing phosphate substitution had to be discontinued once patients consented to study enrolment. The study protocol provided the option of rescue therapy with oral phosphate and active vitamin D, e.g. in case of traumatic fractures or other pending, unplanned surgeries. In these cases, the investigator was to be unblinded regarding the patient's group allocation, and the study medication was to be discontinued. Patients with rescue therapy were to be given the option of remaining in the study and temporarily receiving oral phosphate and vitamin D therapy, but according to the study protocol, the data generated from unblinding onward were to be excluded from the analyses.

The study's primary outcome was the percentage of patients achieving mean serum phosphate levels above the lower limit of normal of 2.5 mg/dL, each measured 2 weeks after the burosumab administration (midpoint of the dose interval). Outcomes on symptoms and adverse events (AEs) were recorded as patient-relevant secondary outcomes.

Unsuitability of the data submitted by the company from the UX023-CL303 study for the benefit assessment

The UX023-CL303 RCT is unsuitable for the present benefit assessment since the study failed to implement the ACT.

For the treatment of adults with XLH, the G-BA specified the ACT of phosphate substitution in conjunction with the administration of calcitriol or alfacalcidol for vitamin D substitution. However, the UX023-CL303 study explicitly excluded the substitution of phosphate and active vitamin D. Under certain conditions, patients had the option of receiving phosphate and active vitamin D in the form of rescue therapy. However, rescue therapy was intended only for patients with an acute event during the placebo-controlled period at which XLH treatment with phosphate and active vitamin D was deemed medically necessary. The restricted use of oral phosphate and active vitamin D as specified in the study hence does not appropriately reflect their use in routine care. The study documents additionally show that phosphate administration was to lead to discontinuation of the study medication. Since no treatment discontinuations occurred in the placebo group during the controlled study phase, patients can be safely assumed to have received no rescue therapy and hence no phosphate substitution.

In the UX023-CL303 study, appropriate reasons for foregoing phosphate substitution as per guideline (substantial increase in parathyroid hormone or secondary hyperparathyroidism) cannot be found to a relevant extent. Consequently, the majority of patients in the comparator arm would have been indicated for phosphate substitution in accordance with the ACT specified by the G-BA.

Overall, the company's approach is not appropriate. The presented data are unsuitable for assessing the added benefit of burosumab in comparison with the ACT specified by the G-BA.

Results on added benefit

No suitable data are available for assessing the added benefit of burosumab in comparison with the ACT in adults with XLH. Hence, there is no hint of an added benefit of burosumab in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 shows a summary of the probability and extent of added benefit of burosumab.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Burosumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Patients with XLH aged 18 years or older[b]	Phosphate substitution[c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. In accordance with the G-BA, patients in the present therapeutic indication are presumed to be symptomatic and hence in need of treatment.
c. In accordance with the G-BA, vitamin D substitution (calcitriol or alfacalcidol) is presumed to be in place.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; XLH: X-linked hypophosphataemia

The G-BA decides on the added benefit.

Supplementary note

The result of this assessment differs from the result of the G-BA's assessment conducted as part of the extension of the therapeutic indication in 2021, where the G-BA determined a minor added benefit of burosumab. In the latter assessment, however, added benefit was regarded as proven on the basis of the approval – irrespective of the underlying data – due to its designation as an orphan drug.

2.2 Research question

The aim of this report is to assess the added benefit of burosumab in comparison with phosphate substitution as the ACT in adult patients with XLH.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of burosumab

Therapeutic indication	ACT[a]
Patients with XLH aged 18 years or older[b]	Phosphate substitution[c]

a. Presented is the ACT specified by the G-BA.
b. In accordance with the G-BA, patients with the present therapeutic indication are presumed to be symptomatic and hence in need of treatment.
c. In accordance with the G-BA, vitamin D substitution (calcitriol or alfacalcidol) is presumed to be in place.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; XLH: X-linked hypophosphataemia

The company formulated a different research question. This is not appropriate, as discussed in the section below. The present benefit assessment was carried out using the ACT specified by the G-BA, phosphate substitution in conjunction with vitamin D substitution (calcitriol or alfacalcidol).

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of added benefit. This concurs with the company's inclusion criteria.

Deviating research question of the company

The company departs from the research question of the present benefit assessment because in its view, 2 patient populations must be distinguished in adults with XLH; these populations differ regarding their response to substitution therapy with oral phosphate and active vitamin D.

According to the company, this results in the following 2 patient populations:

1) Adults who respond to phosphate substitution within 1 year
2) Adults who failed to respond to phosphate substitution within 1 year

In the company's view, response is exhibited mainly by reaching a serum phosphate level in the lower normal range of ≥ 2.5 mg/dL. The company argues that assessing the treatment response additionally requires taking into account any improvement of clinical symptoms (reduced bone and joint pain, improved osteomalacia, reduced fractures and pseudofractures, and improved mineralization of bones and teeth).

Overall, the company presumes that virtually all adults with XLH belong to the subpopulation which fails to respond to phosphate administration (the company's population 2). The company defined BSC as the ACT for the patient population it defined as population 2 because due to

the lack of treatment response and possible side effects, it deems these patients not to be indicated for further phosphate substitution.

Having performed the analysis without the patient population who responded to phosphate substitution within 1 year (the company's population 1), the company did not specify an ACT for this patient population.

Inappropriate approach chosen by the company

The company's approach is inadequate for multiple reasons. First, the evidence provided by the company does not substantiate the response criteria it used (serum phosphate level ≥ 2.5 mg/dL and various symptoms) nor the time limit of 1 year it applied to treatment response. Second, the evidence currently available in the therapeutic indication does not bear out the assumption that symptomatic patients who have not achieved improvement of clinical symptoms under phosphate substitution are generally no longer indicated for further phosphate substitution. No convincing argument in this regard was made by the company either.

For the response criteria, the company cites the guideline available for the present therapeutic indication [3] as well as narrative reviews or expert opinions [4-7], documents from benefit assessments of burosumab by the G-BA [8-10] and by the French Haute Autorité de Santé (HAS) [11], some of which are based on the treatment of children, as well as the publication by Insogna 2018 [12]. Contradicting the company's depiction, the cited literature does not describe serum phosphate levels in the lower normal range as a decisive criterion for response to phosphate substitution in adults with XLH. Some sources even explicitly point out that the treatment goal is not the normalization of the serum phosphate level, but rather symptom improvement [5,7].

The company bases its restriction to 1 year on Carpenter 2011[4] and Lambert 2019 [6] as well as the above-mentioned HAS assessment [11]. While these sources recommend examining the success of substitution therapy after 1 year, they do not recommend treatment discontinuation. The idea of contemplating treatment discontinuation in case of mild symptoms and lack of clinical improvement as described in Carpenter 2011 is based on experience alone. The Haffner 2019 guideline for the present therapeutic indication [3] instead recommends phosphate substitution for all symptomatic adults with XLH unless there is evidence of an increased parathyroid hormone level or secondary hyperparathyroidism.

To support its assumption that none of the patients in the present therapeutic indication respond to phosphate substitution, the company cites the study used for extending the indication for burosumab (UX023-CL303 RCT [12-19], see Section 2.3). The company argues that study participants had already received phosphate substitution at some point in their medical history, but still exhibited disease progression. On this basis, the company reasons that the participants had failed to respond to phosphate substitution and extrapolates this conclusion to the total population of adults with XLH. The company concludes that, given the lack of response and potential side effects, phosphate substitution is unsuitable for these patients. However,

deterioration under therapy is not proof of ineffectiveness. The company has not submitted any further evidence of benefit or harm of phosphate substitution in adults with XLH who have not responded to phosphate substitution within 1 year.

Postulating the absence of treatment alternatives, the company defined BSC as the comparator therapy for the patient population not responding to phosphate substitution within 1 year. As discussed above, however, phosphate substitution is indicated for all symptomatic adults with XLH.

The company's reasoning was therefore rejected. The present benefit assessment is carried out for the entire target population without breaking down the patient population.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on burosumab (status: 2 November 2021)
- bibliographical literature search on burosumab (last search on 2 November 2021)
- search in trial registries / trial results databases for studies on burosumab (last search on 2 November 2021)
- search on the G-BA website for burosumab (last search on 9 November 2021)

To check the completeness of the study pool:

- search in trial registries for studies on burosumab (last search on 17 February 2022); for search strategies, see Appendix A of the full dossier assessment

The check for completeness of the study pool revealed no relevant studies comparing burosumab versus the ACT of phosphate substitution.

This departs from the approach of the company, which included the UX023-CL303 RCT comparing burosumab with placebo in its study pool and used it for the assessment.

The company’s approach is not appropriate. The UX023-CL303 RCT is unsuitable for assessing the benefit of burosumab versus the ACT. This is explained below.

Evidence provided by the company

The company submitted the randomized, double-blind, multicentre UX023-CL303 study comparing burosumab with placebo in adults with XLH. This study enrolled a total of 134 patients aged 18 to 65 years with XLH diagnosis confirmed using biochemical or molecular biology criteria. Additional inclusion criteria were a serum phosphate level < 2.5 mg/dL and the existence of skeletal pain due to XLH and the resulting osteomalacia. The

study excluded patients who had taken phosphate or vitamin D metabolites within 14 days prior to the 2nd screening visit as well as patients with elevated serum calcium levels or increased serum levels of the intact parathyroid hormone.

Patients were allocated in a randomized manner to the study arms of burosumab (N = 68) and placebo (N = 66), stratified by pain intensity (question 5 of the Brief Pain Inventory, average pain[4]) and region (North America / European Union versus Japan versus South Korea). The controlled treatment phase (burosumab versus placebo) had a duration of 24 weeks. Afterwards, patients switched from the comparator arm into the burosumab arm, in which treatment was continued until Week 96. At the US study sites, treatment continuation was allowed, at most until Week 149.

Burosumab or placebo was administered subcutaneously every 4 weeks. The burosumab dosage was 1 mg/kg body weight, not to exceed the maximum dose of 90 mg, and hence was in accordance with the Summary of Product Characteristics (SPC) [20]. Contrary to the SPC, however, at serum phosphate levels above the reference range, the next doses were not withheld until a serum phosphate level below the reference range was measured; instead, the weight-adapted dosage was cut in half if a serum phosphate level of 5.0 mg/dL was exceeded or if 4.5 mg/dL was exceeded 2 consecutive times. Allowed comedications included, in particular, pain medicines at unchanged dosages and treatment regimens. The study disallowed the administration of phosphate or active vitamin D (e.g. calcitriol) for the treatment of XLH, and patients consenting to study participation had to discontinue any existing phosphate substitution. The study protocol provided the option of rescue therapy with oral phosphate and active vitamin D, e.g. in case of traumatic fractures or other pending, unplanned surgeries. In these cases, the investigator was to be unblinded regarding the patient's group allocation, and the study medication was to be discontinued. Patients with rescue therapy were to be given the option of remaining in the study and temporarily receiving oral phosphate and vitamin D therapy, but according to the study protocol, the data generated from unblinding onward were to be excluded from the analyses.

The primary outcome of the study was the percentage of patients achieving mean serum phosphate levels above the lower limit of normal of 2.5 mg/dL, each measured 2 weeks after the burosumab administration (midpoint of the dose interval). Outcomes on symptoms and AEs were recorded as patient-relevant secondary outcomes.

Unsuitability of the data submitted by the company from the UX023-CL303 study for the benefit assessment

The UX023-CL303 RCT is unsuitable for the present benefit assessment since the study did not implement the ACT.

[4]Due to an error in the Interactive Web Randomization System, the study erroneously used question 5 of the BPI (average pain) as the stratification factor. The original plan was to carry out the stratification by BPI question 3 (worst pain).

For the treatment of adults with XLH, the G-BA specified the ACT of phosphate substitution in conjunction with the administration of calcitriol or alfacalcidol for vitamin D substitution. However, the UX023-CL303 study explicitly excluded the substitution of phosphate and active vitamin D. Under certain conditions, patients had the option of receiving phosphate and active vitamin D in the form of rescue therapy. However, this was intended only for patients who had an acute event during the placebo-controlled period for which XLH treatment with phosphate and active vitamin D was deemed medically necessary (e.g. traumatic fracture or unplanned surgical procedure). The restricted use of oral phosphate and active vitamin D as specified in the study hence does not appropriately reflect their use in routine care. The study documents additionally show that phosphate administration was to lead to the discontinuation of the study medication. Since no treatment discontinuations occurred in the placebo group during the controlled study phase, patients can be safely assumed to have received no rescue therapy and hence no phosphate substitution.

Appropriate reasons for foregoing phosphate substitution in accordance with the guideline [3] (substantial increase in parathyroid hormone or secondary hyperparathyroidism) were not found to a relevant extent in the UX023-CL303 study. Symptoms in the form of skeletal pain were an inclusion criterion of the study, and parathyroid hormone levels ≥ 2.5 times the upper reference value were an exclusion criterion. Only 4.5% of patients in the comparator arm exhibited hyperparathyroidism, which was not further differentiated. Consequently, the majority of patients in the comparator arm would have been indicated for phosphate substitution in accordance with the ACT specified by the G-BA.

Overall, the company's approach is not appropriate. The presented data are unsuitable for assessing the added benefit of burosumab in comparison with the ACT specified by the G-BA.

2.4 Results on added benefit

No suitable data are available for assessing the added benefit of burosumab in comparison with the ACT in adults with XLH. Hence, there is no hint of an added benefit of burosumab in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit of burosumab in comparison with the ACT.

Table 5: Burosumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Patients with XLH aged 18 years or older[b]	Phosphate substitution[c]	Added benefit not proven
a. Presented is the respective ACT specified by the G-BA. b. In accordance with the G-BA, patients in the present therapeutic indication are presumed to be symptomatic and hence in need of treatment. c. In accordance with the G-BA, vitamin D substitution (calcitriol or alfacalcidol) is presumed to be in place. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; XLH: X-linked hypophosphataemia		

The assessment described above departs from the company's assessment, which analysed exclusively the population of adults with XLH who do not respond to phosphate substitution within 1 year, deriving a hint of considerable added benefit for this population.

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment departs from the results of the G-BA's assessment conducted as part of the extension of the therapeutic indication in 2021, where the G-BA determined a minor added benefit of burosumab. In the latter assessment, however, added benefit was regarded as proven on the basis of the approval – irrespective of the underlying data – due to its designation as an orphan drug.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a22-12.html.