SMC2514

burosumab 10mg, 20mg and 30mg solution for injection (Crysvita®)

Kyowa Kirin Ltd.

13 January 2023

The Scottish Medicines Consortium (SMC) has completed its initial assessment of the evidence for the above product using the ultra-orphan framework:

Indication under review: Treatment of X-linked hypophosphataemia in adults.

Key points:

- X-linked hypophosphataemia is a rare genetic condition. In adults, symptoms include pathological fractures or pseudofractures with impaired healing, early osteoarthritis, dental problems and an increased risk of osteoporosis. These symptoms are associated with pain and stiffness, may limit physical function and impact quality of life.
- In a phase III study, burosumab significantly increased the proportion of patients achieving mean serum phosphate above the lower level of normal, compared with placebo over 24 weeks of treatment. There is uncertainty relating to the quality of life data.
- Only open-label and uncontrolled data (for less than 3 years of treatment) are available to support burosumab benefits in relation to phosphate levels and symptoms in the long term with continuous treatment. There is uncertainty about long-term efficacy and safety of burosumab, a potentially lifelong treatment, and there are no data to support a mortality benefit with burosumab.
- The submitting company has positioned burosumab for use in symptomatic adult patients (≥18 years old). There is a lack of data against conventional therapy. Uncertainty remains about the relative effectiveness of burosumab against this relevant comparator.
- The cost of burosumab in relation to its health benefits remains high and there are outstanding uncertainties relating to clinical and quality of life data used in the model.

Chair, Scottish Medicines Consortium

SMC ultra-orphan designation

Burosumab has been validated as meeting SMC ultra-orphan criteria:

- Based on a UK epidemiological study, the prevalence of X-linked hypophosphataemia is estimated to be ≤1 in 50,000 of the population in Scotland.
- Burosumab has MHRA GB orphan designation for X-linked hypophosphataemia (PLGB 50262/0001/OD1).
- X-linked hypophosphataemia is chronic and severely disabling due to significant clinical problems, which are lifelong.
- This condition requires highly specialised management.

1. Clinical Context

1.1. Background

Burosumab is a recombinant human monoclonal antibody (IgG1) that binds to and inhibits the activity of fibroblast growth factor 23 (FGF23). This inhibition leads to increased tubular reabsorption of phosphate from the kidney and increased serum concentration of 1,25 dihydroxy-vitamin D.[1-3]

The submitting company requested that burosumab is considered for use in adult patients (≥18 years old) with a confirmed diagnosis of X-linked hypophosphataemia (XLH) who have evidence of progressive disease due to chronic hypophosphataemia and are experiencing persistent and debilitating symptoms.

The indication under review is for the extension of indication to adults. In January 2020 SMC completed its initial assessment, under the ultra-orphan framework, of burosumab 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 (SMC2240).

1.2. Nature of condition

X-linked hypophosphataemia is a rare genetic condition. Affected patients have inactivating mutations in the phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX), which alters phosphate sensing and increases FGF23 leading to chronic renal phosphate wasting, hypophosphataemia and defective bone mineralisation (osteomalacia). In children, XLH manifestations include rickets, bone deformities and impaired growth. In adults, due to a chronic osteomalacia and residual damage from rickets in childhood, the symptomatology is characterised by early osteoarthritis, enthesopathy (calcification of tendons, ligaments and joint capsules), pathological fractures or pseudofractures with impaired healing and an increased risk of osteoporosis. Patients can also suffer from dental problems, in particular, dental abscesses. These manifestations are

associated with pain and stiffness. Hypophosphataemia also causes diffuse symptoms such as weakness and fatigue. These impairments may limit patients' physical function and negatively affect their quality of life.[4-6]

The levels of pain, stiffness and fatigue, experienced by adult patients, impact their mobility, ability to perform daily activities and limits their social, family and work life. These issues can affect their mental health. Household family members of patients with XLH are also often affected with negative effects on their quality of life and mental health.

No other medicines are licensed for this indication. Some symptomatic adult patients are currently managed with conventional treatment, including oral phosphate and active vitamin D analogues. However, evidence supporting improvements of some of the XLH symptoms in adults is limited. In addition, conventional therapy (with daily active vitamin D and at least twice-daily oral phosphate supplements) can be burdensome for patients; it has unpleasant gastrointestinal side effects.[4-6] Clinical experts consulted by SMC considered that burosumab fills an unmet need in this therapeutic area, namely for patients with persistent symptoms and hypophosphataemia despite conventional therapy.

2. Comparative efficacy

Evidence to support the efficacy and safety of burosumab for the treatment of adults with XLH comes from UX023-CL303 (or CL303); study details are summarised in Table 2.1.

Table 2.1 Overview of relevant study [1-4, 7-10]

Criteria	UX023-CL303
Study Design	International, randomised, double-blind, phase III study.
Eligible Patients	The key inclusion criteria were: • Adults aged 18 to 65 years. • Diagnosis of XLH supported by classic clinical features of adult XLH (such as short stature or bowed legs) and at least one of the following at screening: - Documented PHEX mutation in either the patient or in a directly related family member with appropriate X-linked inheritance. - Serum intact fibroblast growth factor 23 (iFGF23) level >30pg/mL by Kainos assay. • Biochemical findings consistent with XLH at Screening Visit (SV) 2 following overnight fasting: - Serum phosphorus <0.81mmol/L. - Ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate (TmP/GFR) of <0.81mmol/L. • Presence of skeletal pain attributed to XLH or osteomalacia, as defined by a score of ≥4 on Brief Pain Inventory (BPI) worst pain. • Estimated glomerular filtration rate (eGFR) ≥60mL/min; or eGFR of 45 to <60mL/min at SV2 with confirmation that the renal insufficiency was not due to nephrocalcinosis.

Treatments	Patients were randomised equally to receive subcutaneously (SC) every 4 weeks for 24 weeks: • burosumab 1mg/kg (each dose was rounded to the nearest 10mg, up to a maximum of 90mg), or • placebo. Oral phosphate and active vitamin D metabolites or analogues were prohibited throughout the study. Following the 24-week period patients could enter continuation and extension periods to receive open-label burosumab.
Randomisation	Randomisation was to be stratified based on mean BPI worst pain score for the 7 days preceding the baseline visit; however, BPI average pain data (>6.0 or ≤6.0) instead of BPI worst pain data were wrongly used to stratify randomisation. Randomisation was also stratified by region (North America/European Union, Japan or South Korea).
Primary outcome	Proportion of patients achieving mean serum phosphorus levels above the lower level of normal (LLN) (0.81mmol/L) at the midpoint of the dose interval (that is weeks 2, 6, 10, 14, 18 and 22), as averaged across dose cycles between baseline and week 24.
Secondary outcomes	Key secondary outcomes, controlled for multiplicity, were: • Change from baseline to week 24 in BPI worst pain score (using the short-form [SF] questionnaire). BPI worst pain item score ranges from 0 (no pain) to 10 (pain as bad as you can imagine). • Change from baseline to week 24 in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) stiffness score. • Change from baseline to week 24 in the WOMAC physical function score. • WOMAC Index physical function and stiffness domains range from 0 (best health) to 100 (worst health).
Statistical analysis	To control the family-wise error rate at the 0.05 level, a hierarchical statistical testing strategy was applied for the primary and three key secondary patient-reported outcomes (PROs; to be tested as a group at 0.05 level with Hochberg adjustment applied) with no formal testing of the key secondary outcomes if the primary outcome was non-significant (that is if p-value was not <0.05 by a two-sided test).

Burosumab significantly increased the proportion of patients achieving mean serum phosphate above the lower level of normal, compared with placebo over 24 weeks of treatment. In the secondary outcomes, burosumab compared with placebo was statistically significant improved only for WOMAC stiffness at week 24. [1-4, 7-10] The observed improvements at week 24 did not achieve the estimated minimal clinically important differences (MCID) for adults with XLH.[4] Results are summarised in Table 2.2 below.

Table 2.2 Primary and key secondary outcomes of UX023-CL303 [1-4, 7-10]

	Burosumab (n=68)	Placebo (n=66)
Primary outcome		
Proportion of patients achieving mean serum phosphate >LLN across midpoints of dose intervals through week 24	94%	7.6%
95% CI	86% to 98%	3.3% to 16%
p-value	<0.001	
Key secondary outcomes[a]		
Change from baseline to week 24 in BPI worst pain score, LS mean difference	-0.79	-0.32
p-value	NS[b]	
Change from baseline to week 24 in the WOMAC stiffness score, LS mean difference	-7.87	+0.25
p-value	<0.0167[c]	
Change from baseline to week 24 in the WOMAC physical function score, LS mean difference	-3.11	+1.79
p-value	NS[d]	

[a] Minimal clinically important differences (MCID) for adults with XLH estimated at: 1.72 for the BPI-SF worst pain score, 9.3 for the WOMAC physical function score and 10.0 for the WOMAC stiffness score; [b] not significant at 0.05 significance level for test; [c] significant at 0.0167 significance level for test (original analysis results); [d] not significant at 0.025 significance level for test

BPI = Brief Pain Inventory; CI = confidence interval; LS = least squares; LLN = lower level of normal; NS = not significant; WOMAC = Western Ontario and McMaster Universities osteoarthritis index

Other Health-Related Quality of Life outcomes were assessed. Overall, as with the key secondary PROs, there was a trend that favoured burosumab in BPI pain severity score; however, there was no meaningful difference between groups in BPI pain interference, Brief Fatigue Inventory (BFI) worst fatigue, BFI global fatigue and Patient's Global Impression of Improvement at week 24.[4]

Healing of active bone fractures or pseudofractures was assessed as an exploratory outcome. At week 24, 43% (28 out of 65 fractures) versus 7.7% (7 out of 91 fractures) of active fractures or pseudofractures had fully healed in the burosumab group compared with the placebo group, respectively.[8]

UX023-CL304 (or CL304) was a supportive international 48-week, open-label, single-arm, phase III study in adults with XLH to assess the effects of burosumab on osteomalacia. Key eligibility criteria were similar to those of CL303. Patients received burosumab 1mg/kg SC every 4 weeks. Oral phosphate and active vitamin D analogues were not allowed and only patients who had not received these in the previous 2 years could be enrolled. The primary efficacy outcome was the percent change from baseline in osteoid volume/bone volume at week 48 based on analysis of iliac crest bone biopsies. Fourteen patients were enrolled, 13 remained in the study and had completed the 48-week open-label treatment period. Evaluable biopsies were available at baseline and week 48 for 11 patients; healing of osteomalacia was observed in all ten evaluable patients. The primary outcome was met; the osteoid volume/bone volume decreased by 54% from baseline to week 48.[1-4, 11]

Open-label continuation and extension data are available from the 24-week treatment continuation period of CL303 (to week 48), the 48-week extension period I of CL303 (to week 96) and the up to 53-week treatment extension period II (up to week 149; in US only). During these periods, continued improvements were seen with burosumab treatment, including some above the MCIDs for WOMAC stiffness by approximately week 36 and for WOMAC physical function beyond week 96. In addition, a 48-week extension study, BUR02, included a subset of patients in Europe who received up to 96 weeks burosumab treatment in CL303 and CL304. Overall, 35 patients enrolled into BUR02 (including 31 from CL303) and had received up to 48 weeks further burosumab treatment as of January 2021. Between the parent studies and BUR02 (range of time between studies: 6 to 26 months), 23 patients received interim burosumab (continuous or partial treatment) and eight did not receive burosumab between studies. Results show that in patients who received interim burosumab between the studies, efficacy improvements seen in CL303 (including in PROs such as BPI-SF worst pain, functional tests and serum phosphate) were maintained through BUR02. However, in those who did not receive interim burosumab, deterioration was seen towards CL303 baseline levels; and with reinitiation of treatment, recovery often took ≥36 weeks. These open-label data support that continued, uninterrupted treatment with burosumab is needed to sustain benefits.[4, 7, 9, 12]

3. Comparative safety

Overall, the safety profile of burosumab in adults was considered in line with the known safety profile in the paediatric population, apart from a potentially higher risk of hyperphosphataemia (reported in about 10% of patients in the adult safety database).[4]

In the 24-week placebo-controlled period of UX023-CL303, any treatment-emergent adverse event (AE) was reported by 94% (64/68) of patients in the burosumab group and 92% (61/66) of patients in the placebo group; these were considered treatment-related in 44% and 39%, respectively. In the burosumab and placebo groups respectively, patients reporting a grade 3 or 4 AE were 12% versus 14% and patients with a reported serious AE were 2.9% versus 3.0% (none were related to treatment). No patient discontinued therapy due to an AE.[4]

The most frequently reported treatment-emergent AEs in the burosumab group versus the placebo group occurred in the following system organ classes: infections and infestations (48% versus 45%) including nasopharyngitis (13% versus 9.1%) and tooth abscess (13% versus 7.6%); musculoskeletal and connective tissue disorders (38% versus 45%) including arthralgia (8.8% versus 24%), back pain (15% versus 9.1%) and pain in extremity (7.4% versus 15%); and nervous system disorders (38% versus 24%) including headache (13% versus 7.6%), restless legs syndrome (12% versus 6.1%) and dizziness (10% versus 6.1%).[4]

4. Clinical effectiveness issues

The key strengths and uncertainties of the clinical evidence are summarised below:

4.1. Key strengths:

- In a robust placebo-controlled randomised phase III study, UX023-CL303, burosumab effects on the normalisation of serum phosphate, a major contributor to the pathophysiology and disease progression of XLH, were considered clinically relevant in a population of symptomatic adults, which is relevant to the submitting company's proposed positioning.[4]
- This was supported by relevant improvements in some important secondary and exploratory outcomes related to patient symptoms:[4]
- The benefits observed with the PROs were modest; but these improvements in patients' experiences of symptom and activity were supportive of the view that burosumab effects are meaningful to patients.
- There is some evidence linking burosumab with improved bone health. CL304 reported improvements in bone mineralisation with burosumab and an exploratory outcomes in CL303 showed a trend to greater healing of active fractures or pseudofractures with burosumab over placebo.[4]
- Burosumab efficacy appeared to be maintained with continuous treatment in open-label continuation and extension studies up to almost 3 years after initiation of treatment.[7, 9, 12]
- Clinical experts consulted by SMC considered that burosumab's place in therapy is for patients with persistent symptoms and hypophosphataemia despite conventional therapy, in whom it is considered a therapeutic advancement as it targets the underlying pathophysiology of XLH.

4.2. Key uncertainties:

- Only placebo-controlled data are available. This comparator was accepted by regulators, because of the practical feasibility of performing a blinded study between burosumab (administered SC every 4 weeks) and conventional therapy (with oral phosphate and active vitamin D analogues given orally several times daily).[4] However, there is a lack of data against conventional therapy, which may be used in some patients. Thus, uncertainty remains about the relative effectiveness of burosumab against this relevant comparator; burosumab is expected to be used in a population insufficiently controlled despite prior use of conventional therapy.
- In CL303, results from the three key secondary PRO outcomes did not achieve the relevant MCIDs at week 24. The placebo-controlled period may have been too short to observe meaningful benefits. In addition, there were some imbalances in baseline characteristics between groups (including in pain intensity and XLH manifestations [such as osteoarthritis], indicating a potentially larger disease burden in the burosumab group), which regulators considered may have had an impact on the key secondary outcomes' analyses. Some

improvements above the MCIDs were seen after week 24 including for WOMAC stiffness (by approximately week 36) and WOMAC physical function (beyond week 96); however, these were observed in an open-label setting and thus should be interpreted with caution.[4]

- Healing of fractures or pseudofractures was an exploratory outcome, uncontrolled for a false positive result, and should also be interpreted with caution. In addition, it is uncertain whether burosumab would prevent new fractures.
- There is uncertainty about the generalisability of CL303 data to the population that may receive treatment in practice. Of note, data are lacking in patients above 65 years old and in patients with renal impairment. While the company's proposed positioning is in patients who may have had prior treatment with conventional therapy, in CL303 the majority of patients (90%) had previously received phosphate plus vitamin D metabolites or analogues.[8]
- XLH is a chronic lifelong condition, but there are no long-term comparative data (the placebo-controlled period of CL303 was only 24 weeks). Longer-term open-label data, for less than 3 years of treatment, are available only in a small number of patients. There is uncertainty about long-term efficacy and safety of burosumab, a potentially lifelong treatment, and there are no data to support a mortality benefit with burosumab.
- Of note, no data are available to support the initiation of burosumab treatment in asymptomatic adults with XLH; however, these patients are outside the submitting company's proposed positioning.
- As expected for this rare condition, the sample size of CL303 (n=134) was small.

5. Impact beyond direct health benefits and on specialist services

Treatment with burosumab is expected to improve XLH symptoms such as fracture healing, pain and stiffness. This would have a positive impact on patients' mobility, enable them to better perform daily activities and continue in employment or education.

The reduction in disabling XLH manifestations may also improve patients' family functioning. The potential improvements in patients' quality of life and mental health may also have a positive impact on their family members.

Administration of burosumab is by SC injection every 4 weeks, which may be preferable to complex multiple oral daily doses of phosphate and vitamin D used in some symptomatic adult patients.

Clinical experts consulted by SMC considered that the introduction of this medicine is not expected to have significant impact on the service delivery. The number of patients that will be treated in practice will be low. Patients would require an increased number of clinic visits but mainly during the initial titration period (estimated at around 3 months).

6. Patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received a joint patient group submission from XLH UK and Metabolic Support UK, which are both registered charities.
- XLH UK has not received any funding from pharmaceutical companies in the past two years. Metabolic Support UK has received 45% pharmaceutical company funding in the past two years, including from the submitting company.
- XLH causes progressively debilitating bone/joint abnormalities along with calcifications of soft tissue, chronic bone pain, fractures, muscle weakness, fatigue, tooth loss, hearing loss, and early-onset arthritis. XLH restricts the ability of patients and caregivers to fully engage in self-care and parenting, as well as pursuing educational and employment opportunities, which in turn adversely affects their emotional wellbeing. XLH has dominant transmission, so younger patients observe and are affected by physical/emotional/economic limitations of older generations.
- There are significant unmet needs. No other treatments tackling the underlying cause of XLH are currently available to adults and current symptom management approaches have limited effectiveness.
- Burosumab provides a potential step change in the management of this disease for adults: it has proven to be superior at reducing the most burdensome symptoms and can be administered in a way that does not impose an additional burden on family members and, by its nature, supports patients to be independent.
- XLH is a progressive disorder, so the sooner a patient receives effective treatment, the better the likelihood they won't become reliant on government disability benefits and other social services. Further, with a more effective treatment, patients see improvements to their emotional wellbeing, and feel less pressure to make unwanted lifestyle decisions (job changes, home relocation or adaptation to accessible bathroom/kitchen or ground floor bedrooms) due to poor health. Similarly, there will be important improvements to the emotional wellbeing of the family/carers. They will worry less about financial issues, also, given that XLH is a genetic disorder, there is frequently more than one family member affected by XLH in a given household. As the patient's health improves with better treatment, the burden on the family drops.

7. Value for money

7.1. Economic case

The submitting company provided an economic case, as described in Table 7.1.

Table 7.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility
Time horizon	Lifetime
Population	The analysis addresses a subgroup of the licensed population (in line with study CL303): adult patients (≥18 years old) with a confirmed diagnosis of XLH, evidence of progressive disease due to chronic hypophosphataemia who are experiencing persistent and debilitating symptoms and who may have had prior treatment with conventional therapy. This is termed the 'symptomatic adult XLH population'.
Comparators	The comparator was a standard of care (SoC) of conventional therapy (oral phosphate and active vitamin D) or no treatments. The submitting company stated that less than half of eligible patients may be treated with conventional therapy at any given time, so that constant or lifelong treatment with conventional therapy is not the standard of care. In the model, the company assumed that 41% of patients, on average, are receiving conventional therapy, based on the Global XLH natural history study (CL001).
Model description	A series of interlinked Markov models were used to evaluate costs and outcomes separately for different age groups and aggregated to provide an overall analysis. Morbidity models were nested within an independent model for overall survival based on published estimates of excess mortality hazard in XLH patients that contrasted survival of XLH patients with matched patients from the Clinical Practice Research Datalink (CPRD) GOLD database.[13] A generalised linear model based on the Global XLH natural history study was developed to predict the incidence of morbidities. Morbidities included kidney stones, fractures, parathyroidectomy spinal surgery, and hyperparathyroidism with further morbidities that were deemed not to be treatable with burosumab included in scenario analyses.
Clinical data	The proportion of patients achieving serum phosphate levels within normal range was based on the primary endpoint in CL303, 94.10% and 7.6% for burosumab and placebo respectively. Conventional therapy was deemed to not provide an improvement in the rate of serum normalization over placebo. A proportion of patients treated with burosumab was assumed to discontinue from treatment after one year due to inadequate response, based on the proportion of patients not achieving clinically meaningful improvement in WOMAC scores at one year of 16%. Patients then discontinued from treatment at a rate of 3% per annum based on expert opinion. The model applied tapering effects at treatment initiation (over one year) and discontinuation (over two years) due to lags in burosumab taking effect and wearing off upon treatment cessation. The incidence of morbidities for patients treated with burosumab and achieving serum phosphate levels within the normal range was deemed to be equivalent to that in the general population when patients continued on treatment. Burosumab was also assumed to have a mortality benefit. The submitting company highlighted uncertainties in the mechanism by which mortality might be increased in XLH, but that these may include decreased physical function and bone deformities. A study by Hawley et al[13] estimated an overall hazard ratio compared to the general population of 2.93 (95% CI 2.8 to 8.1) for patients who were identified using an algorithm classifying likelihood of having XLH. A higher

	estimate was derived for patients deemed likely or very likely XLH of 6.65 (95% CI 1.44 to 30.72) and excess mortality in XLH patients was assumed to be reduced by half with burosumab.
Extrapolation	In CL303, serum phosphate normalisation was maintained through 96 weeks and the model assumed this would persist while patients remained on burosumab.
Quality of life	WOMAC data from CL303 and its open-label extension were mapped to EQ-5D utilities using Wailoo et al (2014)[14]. For the comparator arm, absolute utilities were estimated as a function of age using regression analysis of the CL303 or natural history study data. An incremental time dependent, treatment effect estimated from CL303 was then applied to the comparator utility values to derive utilities for the burosumab arm, independent of the proportion of patients in the normal serum phosphate range. The mean difference in utilities for burosumab vs placebo increased beyond the level seen in the randomised study to around 0.19 after three years based on the open-label extension. Utility multipliers were assigned to modelled morbidities. A disutility for gastrointestinal adverse effects of 0.15 was applied to 56% of patients on conventional therapy. The company considered disutility spillover impairing the quality of life of caregivers, family and friends. The company noted a significant burden on family due to the inherited nature of the condition, meaning that often many close family members will have XLH. The spillover effect on family members is calculated as 20% of the patient benefit of burosumab treatment applied to two family members for the incremental proportion with serum phosphate within normal range and was included in the base case result.
Costs and resource use	Conventional therapy and burosumab medicine costs were included, along with treatment management (administration and monitoring), and costs associated with morbidities. Burosumab costs were based on mean patient weight in the Global XLH natural history study (CL001 with adjustments for increases in serum phosphate concentration above target range [average weight 64.5kg]). Conventional therapy was costed at £395 per treated patient per annum (BNF). Monitoring costs were based on published clinical practice recommendations and morbidity costs were sourced from NHS schedule of costs.
PAS	A PAS was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

7.2. Results

The base case results are presented in Table 7.2. The Quality Adjusted Life Years (QALYs) are primarily driven by the increased survival, reduced adverse effects and on-treatment utility advantages. Incremental costs are primarily a result of differences in costs of medicines acquisition.

Table 7.2 Base case results (PAS prices)

	ICER (£/QALY)
Burosumab	98,554
ICER = Incremental cost-effectiveness ratio, QALY = Quality-adjusted life year, PAS = Patient Access Scheme (PAS)	

7.3. Sensitivity analyses

A number of sensitivity and scenario analyses were provided (Table 7.3).

Table 7.3. Sensitivity and scenario analyses (PAS prices)

		ICER (£/QALY)
1	Utility while on burosumab Year ≥3 on treatment [a]	90,187 - 110,736
2	SoC mortality ratio versus general population [a]	97,441 - 109,599
3	Probability of serum phosphate normalisation on SoC [a]	97,174 - 103,709
4	Spillover effect reduced to one family member	107,878
5	Spillover effect removed (ie patient only perspective)	119,150
6	Decreased mortality reduction for burosumab (25%)	106,647
7	Increased mortality reduction for burosumab (75%)	91,016
8	Burosumab versus '100% no treatment' comparator	106,507
9	Burosumab benefit due to XLH related morbidities is halved	105,074
10	Model additional morbidities (hearing, spinal stenosis, dental abscesses)	97,034
11	Combined analysis: utility while on burosumab at 75% of base case value and decreased mortality reduction for burosumab of 25%	130,248
12	Combined analysis: utility while on burosumab at 75% of base case value and no mortality reduction for burosumab	143,643
13	No mortality benefit with burosumab	119,150
	[a] Sensitivity analysis using confidence limit. ICER = Incremental cost-effectiveness ratio, PAS = Patient Access Scheme (PAS), QALY = Quality-adjusted life year, SoC = standard of care, XLH, X-linked hypophosphataemia.	

7.4. Key strengths:

The economic analysis had a number of strengths, including the choice of appropriate comparator and the coverage of the range of potential starting ages for treatment. Though assumptions as to treatment effectiveness were required for a range of parameters these were clearly stated and included in sensitivity analyses.

7.5. Key uncertainties:

- The impact of treatment on mortality is an assumed proportionate reduction to that of the elevated mortality estimated in the literature. The mechanism for mortality reduction by the medicine was not clear.
- The literature estimate is itself subject to uncertainty both due to difficulties in identifying the most appropriate population and sample size limitations in the selected group. As shown in the sensitivity analysis, reducing or removing the assumed mortality benefit for burosumab resulted in increases in the cost-effectiveness ratio (table 7.3 scenarios 6, 11-13).
- Utility estimates for on- and off-treatment are potentially a key driver of the model. These are mapped from WOMAC data in CL303 and the open-label extension and the on-treatment gain with burosumab is independent of serum phosphate normalisation. The differences shown for burosumab compared to placebo are substantially lower in CL303

than those applied in the model based on continuing improvement in the open-label for burosumab and an assumed constant level for placebo. As shown in sensitivity analysis table 7.3 scenarios 1, 11 and 12, the results are sensitive to the level of quality of life benefits obtained with burosumab treatment.

- Conventional therapy is assumed to provide no clinical benefit in terms of serum phosphate normalisation compared to placebo. While the submitting company pointed to supporting evidence uncertainty remains on this point and discussion at the SMC meeting outlined concerns with the modelled outcomes for the comparator arm. On request, the submitting company did provide some exploratory analysis to show the impact of assuming higher rates of serum phosphate normalisation in the comparator arm, for example if this doubled to 15%, the ICER increased by a small amount to £102,668.
- Achievement of serum phosphate within normal levels is assumed to lead to morbidity rates equivalent to those in the general population, that is, a 100% reduction in excess risk due to XLH. This assumption has not been adequately evidenced. As shown in table 7.3 scenario 9, the results showed some sensitivity to lower levels of reduction in assumed morbidity.

The cost of burosumab in relation to its health benefits remains high and there are outstanding uncertainties relating to clinical and quality of life data used in the model.

8. Costs to NHS and Personal Social Services

The company estimated there would be 23 patients eligible for treatment with burosumab per year, with 5 patients receiving treatment in year one rising to 15 in year five.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

9. Guidelines and protocols

There are currently no Scottish or British guidelines for the management of adults with XLH.

In 2019, a group of European specialists (including in paediatrics, nephrology, orthopaedics and rheumatology) published *Clinical Practice Recommendations for the Diagnosis and Management of X-linked hypophosphataemia*. To reduce osteomalacia and its consequences and to improve oral health, this consensus statement recommends treatment with active vitamin D together with oral phosphorus (phosphate salts) in symptomatic adult patients with XLH (that is, those with musculoskeletal pain, pseudofractures, dental issues, planned orthopaedic or dental surgery or biochemical evidence of osteomalacia with an increase in serum levels of bone-specific ALP). Routine treatment of asymptomatic adult patients is not

recommended. It noted that conventional treatment (with daily active vitamin D and at least twice-daily oral phosphate supplements) is burdensome and has potential adverse effects. The use of burosumab is recommended in adult patients with the following features: persistent bone or joint pain due to XLH or both or osteomalacia that limits daily activities; pseudofractures or osteomalacia-related fractures; and insufficient response or refractory to conventional therapy. Burosumab treatment is recommend to be considered also in patients experiencing complications related to conventional therapy.[5]

In 2022, a working group of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) published a consensus statement on the evaluation, diagnosis and care of patients with X-linked hypophosphataemia. It recommends that treatment in symptomatic adults should include vitamin D analogues alone or with phosphate supplements. Treatment of asymptomatic adult patients is not recommended unless they develop pseudofractures, even without symptoms. The consensus statement recommends that burosumab could be suggested as a second-line therapy in adults with XLH with overt osteomalacia, with pseudofractures that are not responding to conventional treatment or in patients intolerant to conventional treatment. [6]

10. Additional Information

10.1. Product availability date

30 September 2020

10.2. Summary of product characteristics

See the SPC for further information including dosing and safety.

burosumab 10mg, 20mg, 30mg solution for injection (Crysvita®)

Table 10.1 List price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
burosumab	**1mg/kg (rounded to the nearest 10mg up to maximum dose of 90mg) given every 4 weeks by subcutaneous injection**	**272,272**

Costs from BNF online on 04 November 2022. Costs calculated using an adult bodyweight of 70kg. Costs do not take any patient access schemes into consideration.

References

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This assessment is based on data submitted by the applicant company up to and including 09 December 2022.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC assessment report.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When a medicine is available through the ultra-orphan pathway, a set of guidance notes on the operation of the patient access scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC assessment report.

Assessment report context:

No part of the assessment summary on page one may be used without the whole of the summary being quoted in full.

This assessment represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.