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SMC2240

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

Kyowa Kirin Ltd

10 January 2020

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

Key points:

- X-linked hypophosphataemia is a chronic, progressive, debilitating multisystem disease. Affected patients have skeletal abnormalities and the main clinical consequence in children is rickets.
- In short-term (64-week) clinical studies in patients aged 1 to 12 years, burosumab demonstrated greater improvement in a radiological measure of rickets, compared with conventional therapy of oral phosphate and vitamin D.
- Whilst a treatment effect on correction of bone defects in childhood has been shown, it is unclear how this will affect progression of bone disease into adulthood and long-term consequences of X-linked hypophosphataemia.
- Some short-term data on quality of life are available but are difficult to interpret.
- An economic evaluation projected significant improvements in quality-adjusted life years over a patient's lifespan compared with conventional therapy. However, there were uncertainties particularly surrounding quality of life estimates and an assumed ongoing response to burosumab.
- Despite a Patient Access Scheme (PAS), the treatment's cost in relation to its health benefits remains high.

Chairman, Scottish Medicines Consortium

Indication

Treatment of X-linked hypophosphataemia with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons.[1]

Dosing Information

The recommended starting dose is 0.8mg/kg, given every two weeks by subcutaneous injection. The maximum dose is 90mg. All doses should be rounded to the nearest 10mg.

Oral phosphate and vitamin D analogues should be discontinued 1 week prior to initiation of treatment. At initiation, fasting serum phosphate concentration should be below the reference range for age.

After initiation of treatment with burosumab, fasting serum phosphate should be measured every 2 weeks for the first month of treatment, every 4 weeks for the following 2 months and thereafter as appropriate. Fasting serum phosphate should also be measured 4 weeks after any dose adjustment. If fasting serum phosphate is within the reference range for age, the same dose should be maintained.

To decrease the risk of ectopic mineralisation, it is recommended that fasting serum phosphate is targeted in the lower end of the normal reference range for age.

Further details are included in the Summary of Product Characteristics (SPC).[1]

Treatment should be initiated by a physician experienced in the management of patients with metabolic bone disease.

Product availability date

January 2019.

Burosumab has conditional marketing authorisation from the European Medicines Agency (EMA).

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 EMA orphan designation for the treatment of hypophosphataemic rickets (EMA/51018/2018).

- X-linked hypophosphataemia is chronic and severely disabling due to significant clinical problems in bone formation during childhood, with associated skeletal deformities, including rickets.
- This condition requires highly specialised management.

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 fibroblast growth factor 23 (FGF23) leading to hypophosphataemia. X-linked hypophosphataemia is a chronic, progressive, debilitating, multisystem condition that severely impacts day to day functioning and health-related quality of life. Patients with X-linked hypophosphataemia have skeletal abnormalities and the main clinical consequences in children are rickets, lower limb deformities, growth retardation and disproportionately short stature. Patients may also have symptoms such as dental abscesses, hearing loss, headaches, muscle weakness, pain, stiffness, and fatigue.[2, 3]

Patients have mobility problems and may be unable to participate in activities such as sports which, along with an altered physical appearance, have a negative psychological impact, particularly on children. Due to the genetic nature of the condition, family members may also be affected meaning the caregiver could also be suffering from the condition further increasing the family burden. In a significant proportion of patients surgery is required to correct skeletal deformities, which would require time off school and impact on learning and potential career options.

Currently patients with X-linked hypophosphataemia receive conventional treatment with phosphate and vitamin D supplements. Whilst early treatment can improve rickets, severe skeletal abnormalities usually remain, and phosphate and vitamin D do not treat the underlying condition. Adherence to therapy is difficult due to need for frequent dosing of phosphate supplements (often 4 to 6 times a day) and adverse effects such as gastrointestinal symptoms. Vitamin D can result in hypercalcaemia and kidney stones. In addition, conventional therapy further stimulates FGF23 levels which may limit efficacy. Clinical experts consulted by SMC confirmed that there is an unmet need in this therapeutic area.

New technology

Burosumab is the first disease-modifying biologic treatment to target the pathophysiology of X-linked hypophosphataemia. It is a recombinant human monoclonal antibody (IgG1) that inhibits the activity of FGF23, which increases tubular reabsorption of phosphate from the kidney and increases serum concentration of 1, 25 dihydroxy-vitamin D. The aim of treatment is to achieve normal serum phosphate levels and therefore decrease the clinical consequences of X-linked hypophosphataemia.[1, 2]

Impact of new technology

Comparative efficacy

Key evidence for this indication is from CL301, an ongoing, randomised, active-controlled, open-label, phase III study in children aged 1 to 12 years with X-linked hypophosphataemia. Recruited patients had confirmed PHEX mutation or a family member with appropriate X-linked dominant inheritance. Fasting serum phosphorus was lower than 0.97mmol/L and total Thacher rickets severity score was ≥2. Patients had received conventional therapy (with oral phosphate and vitamin D) for at least 6 consecutive months (children younger than 3 years) or at least 12 consecutive months (children older than 3 years). The Thacher rickets severity score is a validated assessment which assigns a total score ranging from 0 (no rickets) to 10 (severe rickets). This total score is based on the sum of scores for the wrist (0 to 4) and knee (0 to 6). The EMA noted that the total score in X-linked hypophosphataemia typically does not exceed 4.[4]

Before randomisation, all patients underwent a 7-day washout period, in which patients stopped treatment with conventional therapy. Patients were randomised equally to burosumab (n=29) or conventional therapy (n=32) consisting of oral phosphate and alfacalcidol or calcitriol for 64 weeks.

The initial dose of burosumab was 0.8mg/kg subcutaneously every 2 weeks, increased to 1.2mg/kg every 2 weeks if two consecutive pre-dose, fasting, serum phosphorus concentrations were below 1.03 mmol/L and serum phosphorus had increased by less than 0.16 mmol/L from baseline on a single measurement. Conventional therapy comprised oral phosphate (20 to 60 mg/kg per day divided into three to five doses) and alfacalcidol (40 to 60 nanograms/kg per day) or calcitriol (20 to 30 nanograms/kg per day), given one to three times a day depending on formulation.[4]

The primary outcome was the change in rickets severity at week 40, assessed by the Radiographic Global Impression of Change global score; a 7-point ordinal scale with scores of -3 (severe worsening), -2 (moderate worsening), -1 (minimal worsening), 0 (unchanged), +1 (minimal healing), +2 (substantial healing), and +3 (complete healing). This was based on skeletal abnormalities on wrist and knee radiographs assessed by three independent paediatric radiologists.

Patients in the burosumab group had significantly greater improvement in rickets as assessed by the Radiographic Global Impression of Change global score at week 40 and week 64 compared with those in the conventional therapy group. In addition, substantial healing of rickets, defined as Radiographic Global Impression of Change global score ≥2, was achieved by

72% (21/29) of patients in the burosumab group compared with 6.2% (2/32) of patients in the conventional therapy group.[4]

Selected secondary outcomes detailed in Table 1 below favoured burosumab over conventional therapy. Phosphate levels of patients in the burosumab group increased to the lower limit of normal whereas there were minimal changes in the conventional therapy group.

Table 1. Primary outcome (at week 40) and selected secondary outcomes (at week 64) from study CL301.[4, 5]

		Burosumab (n=29)	Conventional therapy (n=32)	Difference between groups (95% CI)
LS mean Radiographic Global Impression of Change global score at week 40[a]		1.9	0.8	1.1 (0.8 to 1.5) p<0.001
LS mean Radiographic Global Impression of Change global score at week 64[a]		2.1	1.0	1.0 (0.7 to 1.3)
LS mean change from baseline in total Thacher rickets severity score	Baseline	3.2	3.2	
	Change	-2.2	-1.0	-1.2 (-1.6 to -0.8)
LS mean Radiographic Global Impression of Change lower limb deformity score[a]		1.3	0.3	1.0 (0.6 to 1.4)
LS mean change from baseline in recumbent length and standing height Z score	Baseline	*	*	
	Change	0.17	0.02	0.14 (0 to 0.29)
LS mean change from baseline in the mean percent predicted normal in 6 minute walk test[b]	Baseline	65%	76%	
	Change	9%[c] (n=13)	2%[c] (n=20)	7% (0.01 to 14.52)

CI: confidence interval, LS: least squares, N/A: not applicable, [a]provides one score therefore no baseline measurement, [b]performed in patients aged ≥5 years and able to complete, [c]adjusted for baseline differences

Health-related quality of life was measured in study CL301 but results are marked as academic in confidence by the company and cannot be presented here.

Patients who completed the 64-week, active-controlled period were eligible to enter the extension phase and receive up to an additional 76 weeks of open-label burosumab.[4] Efficacy results are awaited.

CL201 was an open-label, phase II study that recruited children aged 5 to 12 years of age with a diagnosis of X-linked hypophosphataemia (n=52). Eligible patients had active rickets at growth plates, bowing of the femur or tibia, or both and their pubertal stage was classified as Tanner stage 2 or lower. The final 16 recruited patients were required to have a Thacher rickets severity score of at least 1.5 at the knee. They were randomly assigned equally to receive subcutaneous burosumab, at an initial dose of either 0.1mg/kg to 0.3mg/kg every 2 weeks (n=26) or 0.2mg/kg to 0.6mg/kg every 4 weeks (n=26). The dose was adjusted to achieve a serum phosphorus level at the low end of the normal range. The primary outcome, change in Thacher rickets severity total score, was -1.1 and -0.7 at week 40 in the 2-weekly and 4-weekly dosing groups respectively ($p<0.001$ for both comparisons). The Radiographic Global Impression of Change score at week 40 was 1.6 in both groups. These results indicated improvements in rickets in both groups at week 40 and this was maintained at week 64.[2, 6] Improved functional ability and decreased pain, as assessed by the Pediatric Orthopedic Society of North America – Pediatric Outcomes Data Collection Instrument (POSNA-PODCI) questionnaire, was shown in the overall population at 64 weeks.[2, 6] This study included a 96-week extension phase. All patients continued into the extension phase and received burosumab every 2 weeks.[7]

Study CL205 was an open-label phase II study that recruited children aged 1 to 4 years of age with X-linked hypophosphataemia (n=13). At least five patients were required to have a Thacher Rickets Severity Score at the knee of at least 1.5 at screening. Patients received burosumab 0.8mg/kg by subcutaneous injection every 2 weeks increased to 1.2mg/kg every 2 weeks if two consecutive pre-dose serum phosphorus concentrations were below 1.03mmol/L, serum phosphorus had increased by <0.16mmol/L from baseline, and a dose had not been missed. Treatment continued for 64 weeks. Safety and change from baseline to week 40 in fasting serum phosphorus concentration were the co-primary outcomes. The mean fasting serum phosphorous concentration increased from 0.81mmol/L to 1.12mmol/L. The least squares mean increase from baseline of 0.31mmol/L was significant, $p<0.001$. Total Thacher rickets severity score decreased by least squares mean of -2.0 from baseline to week 64. The Radiographic Global Impression of Change least squares mean score was +2.2 at week 64 also indicating improvement. In addition, all patients achieved substantial healing of rickets (defined as a Radiographic Global Impression of Change Score ≥+2.0) by week 40.[8]

Burosumab has a conditional marketing authorisation from the EMA. To confirm the efficacy and safety of burosumab the Marketing Authorisation Holder is required to submit updated results of studies CL201 and CL205, by July 2019 and May 2020, respectively. In addition, they were required to conduct the phase III study, CL301 (described above), versus oral phosphate and vitamin D in paediatric patients with X-linked hypophosphataemia, by July 2019.[2]
*Other data were also assessed but remain confidential.**

Comparative safety

In study CL301 treatment emergent adverse events were reported in 100% (29/29) of patients in the burosumab group and 84% (27/32) of patients in the conventional therapy group. Adverse events were considered related to study treatment in 59% (17/29) and 22% (7/32) of patients respectively. No serious, treatment-related adverse events were reported. Grade 3 or 4 adverse events occurred in 14% (4/29) and 9.4% (3/32) of the respective groups. There were no adverse events leading to study discontinuation, treatment discontinuation, or death.[4, 5]

The most common adverse events were pyrexia (55% and 19%), cough (52% and 19%), arthralgia (45% and 31%), vomiting (41% and 25%), nasopharyngitis (38% and 44%), pain in extremities (38% and 31%), headache (34% and 19%), injection site erythema (31% and 0), dental caries (31% and 6%), tooth abscess (28% and 9%), rhinorrhoea (24% and 6%), diarrhoea (24% and 6.2%) and vitamin D decrease (21% and 3.1%).[4] Pre-defined adverse events of interest that occurred more commonly in the burosumab group compared with conventional therapy included injection site reaction (52% and 0) and hypersensitivity (38% and 19%). No patients in either group developed hyperphosphataemia. There were minimal changes in plasma intact parathyroid hormone, serum calcium, urine calcium excretion or nephrocalcinosis scores in both groups.[4]

Clinical effectiveness issues

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

Key strengths:

- In the key phase III study, CL301, patients in the burosumab group had a significantly greater improvement in rickets, as assessed by the Radiographic Global Impression of Change global score at week 40, compared with those in the conventional therapy (oral phosphate and vitamin D) group. The improvement was maintained at week 64.
- In addition, substantial healing of rickets, defined as Radiographic Global Impression of Change global score ≥2 was achieved by 72% of the burosumab group compared with 6.2% of the conventional therapy group.[2, 4]
- Greater improvements with burosumab versus conventional therapy were also demonstrated for the key secondary outcomes at week 64 including change in Thacher rickets severity score and lower limb deformity score. In addition, burosumab was associated with greater improvements in growth (standing height/recumbent length) and walking ability (6 minute walk test).
- Clinical experts consulted by SMC viewed burosumab as a therapeutic advancement. While long-term evidence is lacking, they anticipate a reduction in long-term complications of X-linked hypophosphataemia. In-line with European clinical practice recommendations published in May 2019, they suggest that use of burosumab would be considered in

children and adolescents with disease that is refractory to conventional therapy, and in patients unable to adhere to or experiencing complications of conventional therapy. [3]

Key uncertainties:

- X-linked hypophosphataemia is a chronic lifelong condition however data on the impact of burosumab on the long-term consequences of X-linked hypophosphataemia are not available.
- Controlled data demonstrate a treatment effect of burosumab on correction of bone defects in childhood, but it is unclear how this would affect progression of bone disease into adulthood, patient-relevant outcomes and impact on quality of life.
- While some short-term data on quality of life are available, the magnitude of effect and clinical relevance of improvements are difficult to interpret.
- Burosumab is licensed for use in children and adolescents with growing skeletons (until growth plates fuse). While the extension phase of studies CL201 and CL301 will include some patients slightly older than 12 years, no clinical trial evidence in patients who commence treatment between the ages of 13 to 17 years is available. It is possible this group may respond differently due to puberty and bone maturity.
- Only patients with total Thacher rickets severity score of at least 2 were recruited to study CL301. Patients with milder severity of X-linked hypophosphataemia (Thacher score of at least 1.5) were included in phase II studies, however there is no comparative evidence versus conventional therapy in these patients.
- Small patient numbers were included in the key study, although it is acknowledged that X-linked hypophosphataemia is a rare condition and burosumab is an ultra-orphan medicine, therefore small patient numbers are inevitable.

Overall, the clinical case was considered reasonable in the short term when burosumab is likely to provide improvement of rickets in children and adolescents with X-linked hypophosphataemia. However, there is some uncertainty about efficacy in patients aged between 13 and 17 years, the effect on progression of bone disease into adulthood and on the long-term consequences of X-linked hypophosphataemia. The impact on patients and families in the longer term remains unclear.

Impact beyond direct health benefits and on specialist services

Treatment with burosumab is expected to reduce skeletal deformities and potentially other symptoms such as pain and fatigue. This would have a positive impact on patients' attendance and performance at school, improve their ability to enter further education and increase their choice of employment. Patients may require less care and less corrective surgery, which would reduce the impact on family/carers, increasing their ability to work and participate in family

activities. These wider benefits were not captured in the economic evaluation submitted by the company.

Administration is by subcutaneous injection every 2 weeks which may be preferable to complex multiple oral daily doses of phosphate and vitamin D. Clinical experts note that patients will be required to attend hospital for monitoring and, initially, for administration of the injection.

Patient and carer involvement

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

- We received a joint patient group submission from X-linked hypophosphatemia (XLH) UK and Metabolic Support UK, which are both registered charities.
- XLH UK has not received any pharmaceutical company funding in the past two years. Metabolic Support UK has received 15.3% pharmaceutical company funding in the past two years, including from the submitting company.
- X-linked hypophosphataemia is a hereditary disorder where children and adults develop abnormalities in the bones and joints. Often complex orthopaedic surgery is needed in childhood which is traumatic for children and their parents. While X-linked hypophosphataemia is not life threatening, its burden is lifelong. Patients and carers report that living with, or caring for, someone with X-linked hypophosphataemia can have a dramatic and detrimental impact on their physical and mental health, limiting their ability to participate in everyday activities such as cooking and cleaning and also on education, employment and emotional wellbeing. Due to the hereditary nature of X-linked hypophosphataemia, the burden on the family can be even greater when siblings and parents are also affected.
- The current treatment available is oral phosphate dissolved in water, which is taken 4-6 times a day with an activated vitamin D tablet. This can be difficult to tolerate due to its unpleasant taste and the disruption frequent administration causes to daily routines. It can also cause side-effects such as upset stomach, diarrhoea and kidney stones.
- If burosumab can help patients maintain normal levels of phosphorous for longer periods of time, it could prevent life-changing complications and improve the overall long-term quality of life for the patients and their families.
- With the potential for better treatment in childhood this could result in improved outcomes for patients as they approach adulthood. By reducing the debilitating physical symptoms of X-linked hypophosphataemia and avoiding traumatic corrective surgery and use of braces in childhood, patients may have improved mental health as adults. It could also mean that patients may no longer need to make life changing decisions (such as job changes and home relocation) due to poor health, and could help to alleviate the social and emotional burden of the disease in later life.

Value for money

The submitting company presented a cost-utility analysis evaluating burosumab versus conventional therapy 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. Conventional therapy was defined as the use of oral phosphate (Phosphate Sandoz) and activated vitamin D (alfacalcidol).

A five-state Markov model was developed to model the costs and consequences for eligible patients over a lifetime horizon. Four of the health states were used to model rickets severity, based on Thacher rickets severity score (RSS). At model entry, 1000 patients were distributed across the health states according to the corresponding baseline RSS from the pooled CL201, CL205 and CL301 studies; a mean starting age of 6.8 years was also derived from these studies. Patients could remain within each health state (healed: RSS 0; mild: RSS 0.5 – 1.0; moderate: RSS 1.5 – 2.0; severe: ≥2.5) or transition to the absorbing health state of death at any point until the age of 18. Disease severity thresholds were adapted from a previous publication reporting seven severity levels.[9] A perspective of NHS Scotland and social care was taken, and a one year cycle length was applied.

Clinical effectiveness data were estimated by pooling data from the randomized CL301 study with the CL201 and CL205 dose-finding studies, to derive an annualised transition probability matrix for burosumab. The placebo arm of the CL301 study was pooled with data from a UK retrospective chart review to estimate transition probabilities for conventional therapy. Patients were distributed across the health states based on pooled baseline demographics from the three burosumab studies, and the annualised transition probabilities applied to assume a constant rate of response until the age of 18. After the age of 18, patients were assumed to maintain the same level of rickets severity until death. Scottish National Life Tables were used to apply general population mortality.

Health state utility values were derived from a multi-stage vignette study.[10] Vignettes were developed through interviews with clinical experts, to cover a mixture of ages and age ranges (1-4; 5-12; 13-17; 18 years; 40 years; 60 years) and rickets severity scores (healed; mild; moderate; severe). Five clinical experts then estimated the expected EQ-5D-5L dimension scores for each of the vignettes, before the UK 'crosswalk' algorithm was applied.[11] This resulted in a wide range of utility estimates from 0.91 (age 5-12, healed) to 0.282 (age 60, severe). A 'last observation carried forward' approach was used to estimate utilities between the adult ages derived in the vignette study, and age-adjustment was applied. Disutility was not applied for adverse events, disease complications or downstream surgical interventions.

Medicines acquisition costs were included for burosumab and conventional therapy. The burosumab dose was based on the Summary of Product Characteristics, and assumed that

patients escalated from 0.4mg/kg to a dose of 0.8mg/kg for the majority of the time horizon. The costs of administration, adverse event management, and wastage were not included. In the base case, burosumab treatment was assumed to continue until the age of 14 for females and 16 years for males. A scenario analysis was used to test an increased treatment duration. Health state costs were applied according to disease severity levels, comprising costs of surveillance, drug costs, pain and mobility costs and orthopaedic interventions.

A patient access scheme was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland.

Base case results are summarised below in terms of PAS price (Table). Treatment costs with burosumab represented the main contributor to incremental costs, while a Markov trace highlighted that the majority of QALY gains are likely to come from nearly all burosumab patients entering and remaining in the 'healed' health state across the time horizon.

Table 2: Base case results versus conventional therapy – with PAS

Technologies	**ICER (£/QALY)**
Burosumab	126,931

ICER: Incremental cost-effectiveness ratio, QALY: quality-adjusted life year

A number of scenario analyses were obtained during the course of the assessment. The key scenarios are presented below (Table 1). These highlight that the model is highly sensitive to the approach to extrapolating transition probabilities to the age of 18, the utility associated with the 'healed' health state and the assumption of a lifetime treatment effect.

Table 1: Scenario analyses -with PAS

	Base case assumption	**Scenario assumption**	**ICER (£/QALY)**
		Base case	126,931
1.	Stopping rule based on TA188 (females: 14 years; males: 16 years)	Alternative stopping criterion (females: 16 years; males: 17 years)	155,326
2.	Transition probabilities from CL301 study and UK chart review	Transition probabilities for conventional therapy taken from CL002 study	142,986

3.	'healed' patients have separate utility and costs to 'mild' patients	'Healed' utility and costs equivalent to 'mild' utility and costs	319,255
4.	Burosumab dose based on normal SPC dose	Burosumab average dose adjusted for observed data from CL301 study	143,344
5.	Constant transition probabilities to age 18	Removal of extrapolated transition probabilities (to age 18)	269,524
6.	Lifetime time horizon	Time horizon: 10 years	440,863
7.		Time horizon: 20 years	240,996
8.	Lifetime treatment effect	Treatment waning: 30 years	151,237
9.		Treatment waning: 50 years	134,395
10		Treatment waning: 70 years	128,497

ICER: Incremental cost-effectiveness ratio, QALY: quality-adjusted life year; SPC: Summary of Product Characteristics

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

Key strengths:

- Randomised controlled studies are available to support the estimation of treatment effectiveness, providing evidence of a relative benefit over the study period.
- A number of additional data sources have been provided which support understanding of the natural history of the disease, as well as attempting to quantify the quality of life impact of X-linked hypophosphataemia at various stages of a patient's life.
- A number of analyses are provided such as summaries of dissagregated costs, Markov traces, a range of scenario analyses and deterministic and probabilistic analyses, which enable identification of the key model drivers.

Key uncertainties:

- **Structure:** The model structure utilises RSS scores as an indicator of disease severity. The severity levels appear to have been based on the availability of data and it is unclear whether these thresholds adequately reflect changes in patient utility and healthcare requirements. Additionally, the RSS may not capture other important aspects of the condition which are reflected in other measures (such as the Radiographic Global Impression of Change).

- **Clinical evidence sources:** No efficacy data are available for burosumab in patients who initiate treatment between the ages of 13 to 17 years old. The model assumes an equivalent level of benefit to patients who initiate treatment at an earlier age, although an SMC clinical expert suggesting earlier treatment may be beneficial. Additionally, transition probabilities are pooled from multiple clinical studies and the rarity of the condition precluded adjustment for age, baseline disease severity and other potential confounding factors. The process of deriving separate transition probability matrices for burosumab and conventional therapy also breaks the randomisation of the CL301 study, creating a naïve comparison and introducing uncertainty into the level of relative benefit.
- **Extrapolation of clinical benefits:** two assumptions are made regarding the extrapolation of clinical benefits for burosumab. Annualised transition probabilities (derived from 64 week follow-up data) are assumed to remain constant up to the age of 18 years, despite evidence of a stabilisation of RSS scores beyond 64 weeks. The model also assumes that disease severity stabilises from age 18, leading to nearly all burosumab patients remaining in the 'healed' state until death. The use of more conservative approaches regarding transition probabilities (Scenario 5) and duration of treatment effect highlight significant uncertainty in these assumptions (Scenarios 8 – 10).
- **Utility estimates:** the process of estimating utility did not involve patients with X-linked hypophosphataemia or their caregivers and, although based on interviews with clinical experts, may not fully reflect the impact of the condition on a patient's day-to-day quality of life. Approaches to estimating utility over the longer-term may also overestimate the utility at different stages of adulthood. As indicated in Scenario 3, the utility estimates are subject to significant uncertainty; consideration of patient-derived EQ-5D-Y and EQ-5D outcomes for children and adults, and potentially caregiver-reported EQ-5D, would be preferable.
- **Treatment costs:** the key driver of incremental costs is the acquisition cost of burosumab, with increases in the average dose requirements and duration of treatment resulting in significant increases in the ICER (Scenarios 1 and 4). Further real-world data on treatment utilisation would be beneficial.

The cost of burosumab in relation to its health benefits remains high, and there are a number of outstanding uncertainties relating to the incremental clinical and patient benefits over the longer-term.

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

Costs to NHS and Personal Social Services

The submitting company estimates that there will be around 14 patients eligible for treatment with burosumab each year, with 5 patients receiving treatment in year 1 and 12 patients in year 5.

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.**

Additional information: guidelines and protocols

Currently there are no Scottish or British guidelines for the management of X-linked hypophosphataemia. In 2019 a group of European specialists (in paediatrics, nephrology, orthopaedics and rheumatology) published: Clinical Practice Recommendations for the Diagnosis and Management of X-linked hypophosphataemia. The consensus statement provided recommendations for the use of standard therapy and the use of the newly introduced burosumab. When a diagnosis is given the first line treatment for children aged one and older and in adolescents with X-linked hypophosphataemia should include oral phosphate and vitamin D. The standard treatment has been criticised for the complex dosing schemes and unpleasant side effects. In addition the long term benefits of this regimen is questionable. The use of burosumab should be considered in the following clinical situations: radiographic evidence of overt bone disease; poor response or complications to standard therapy; and an inability to adhere to standard therapy. The recommendations also highlights that individuals should not be taking any additional medications and removal of all phosphate modifying medications should begin at least one week prior to commencing treatment of burosumab.[3] This recommendations predate the availability of results from study CL301.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
burosumab	**Starting dose: 0.4mg/kg Normal maintenance dose: 0.8mg/kg given every two weeks by subcutaneous injection.**	**77,792 to 466,752**
phosphate (Phosphate Sandoz) and alfacalcidol	Phosphate Sandoz: 4 to 6 tablets daily or 2 to 3 tablets daily for under 5 years, adjusted as necessary. Alfacalcidol: 1 month to 11 years: 25 to 50 nanograms/kg/day 12 to 17 years: 1 microgram daily	201 to 529

Doses are for general comparison and do not imply therapeutic equivalence. Costs for burosumab from eMC Dictionary of Medicines and Devices Browser and phosphate and alfacalcidol from BNFc on 01/11/19. Costs for burosumab are based on the normal maintenance dose described in the SPC and for phosphate and alfacalcidol doses are from BNFc, estimated for patient weight 10kg to 70kg. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

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This assessment is based on data submitted by the applicant company up to and including 13 December 2019.

**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: http://www.scottishmedicines.org.uk/About_SMC/Policy*

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.