NICE National Institute for Health and Care Excellence

NICE guidance

Burosumab for treating X-linked hypophosphataemia in adults

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Burosumab is recommended, within its marketing authorisation, as an option for treating X-linked hypophosphataemia (XLH) in adults. Burosumab is only recommended if the company provides it according to the commercial arrangement.

Why the committee made these recommendations

Usual treatment for XLH in adults is oral phosphate and active vitamin D. Burosumab is used in the NHS for treating XLH in people under 18; this evaluation is for treating XLH in adults.

Clinical trial evidence shows that burosumab increases the level of phosphate in the blood more effectively than placebo. The evidence also suggests that people having burosumab may have less pain and fatigue, and improved physical functioning compared with placebo in the short term, but this is uncertain.

Although there are some uncertainties in the economic model, the cost-effectiveness estimates are within the range considered an acceptable use of NHS resources. So, burosumab is recommended.

2 Information about burosumab

Marketing authorisation indication

2.1 Burosumab (Crysvita, Kyowa Kirin) is indicated for 'the treatment of X-linked hypophosphataemia in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease, and in adults'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for burosumab.

Price

2.3 The list prices per vial of solution for injection are £2,992 for 10 mg/1 ml, £5,984 for 20 mg/1 ml, and £8,976 for 30 mg/1 ml (excluding VAT; BNF online accessed November 2023).

2.4 The company has a commercial arrangement. This makes burosumab available to the NHS with a discount. The size of the discount is commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence submitted by Kyowa Kirin, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

XLH is a rare condition

3.1 X-linked hypophosphataemia (XLH) is a rare, genetic, progressive condition. In England, around 300 adults may have XLH, but including unregistered and undiagnosed XLH that figure would be closer to 1,000 adults. XLH is an X-linked dominant condition that is caused by mutations in the PHEX gene that inactivate the PHEX enzyme. This leads to errors in phosphate sensing and increased levels of fibroblast growth factor 23 (FGF23). Excess FGF23 causes impaired phosphate conservation and excessive phosphate excretion. It also supresses vitamin D production, which causes reduced calcium and phosphate absorption. After consultation, the committee noted that there may be fewer than 1,000 adults with XLH who would be eligible for burosumab. Because XLH is a genetic condition, it often affects several members of a family.

Effects on quality of life

3.2 Symptoms generally start in childhood. For adults, symptoms include osteomalacia (soft, weak bones), bone pain, fractures, pseudofractures, joint stiffness, restricted movement, neurological complications, hearing impairments, spinal cord compression, dental problems, muscle weakness and fatigue. A clinical expert added that people may develop hyperparathyroidism, which can lead to cardiovascular and kidney complications. The patient experts said that pain is a large part of living with XLH and managing the excruciating, radiating bone pain often involves using opioids. They explained that to try to avoid pain, people with XLH will restrict their movement, which causes their muscles to

stiffen up, reducing mobility. Reduced mobility can make it more difficult to manage weight. The patient experts added that because XLH is a genetic condition, people with XLH may also be a carer for family members who may have more severe symptoms. The carers may have to stop work to do this. The company highlighted that XLH may be associated with an increased likelihood of lower socioeconomic status for people with the condition. This is because of the limitations on ability to work, and for their carers who may also have XLH. The committee concluded that XLH has a large impact on quality of life and the ability to do day-to-day activities and work.

Clinical management

Treatment pathway

3.3 The company positioned burosumab as a second-line treatment option for adults with symptomatic XLH, after conventional treatment, which consists of oral phosphate and active vitamin D. The clinical experts explained that the aim of using oral phosphate is not to normalise serum phosphate levels. This is because the doses needed for normalisation are generally intolerable, with side effects such as diarrhoea, which substantially affects people's ability to do day-to-day activities, and hyperparathyroidism, which can cause permanent kidney damage. Oral phosphate also has other issues, including its bad taste, and the need to take it multiple times a day, meaning serum phosphate levels may fluctuate throughout the day. A clinical expert explained that some people can tolerate conventional treatment. But for most people with XLH, the side effects of conventional treatment cause them to stop treatment. The consequent untreated XLH results in further complications from low phosphate levels. The patient experts agreed that conventional treatment is ineffective at managing XLH, and many people find the treatment intolerable. Both patient experts were having burosumab and said that it had been a 'game changer' for them, reducing pain and resulting in a positive behavioural cycle of being able to move more and feel less stiff, with accompanying weight loss. The committee concluded that there is an unmet need for a well-tolerated treatment that normalises phosphate levels in adults with XLH.

Treatment population

3.4 The population in the NICE scope was adults with XLH. The company focused on a narrower population than the marketing authorisation: people 18 years and over with confirmed XLH and chronic hypophosphataemia symptoms that include a Brief Pain Inventory (BPI) 'worst pain in last 7 days' score of at least 4, with conventional treatment being unsuitable because of ineligibility, intolerance or insufficient efficacy. The clinical experts agreed that the BPI is a reproducible assessment tool in clinical practice that can be easily documented. The company confirmed that there are 3 potential subgroups of its treatment population:

- People 18 years and over who would have burosumab for the first time in adulthood (the population the company provided evidence for).
- People who have had burosumab when under 18 years, and stopped treatment when their bones stopped growing, in line with NICE's highly specialised technologies guidance on burosumab for treating XLH in children and young people.
- People who have had burosumab when under 18 years, and stopped treatment for reasons other than their bones no longer growing.

  The clinical experts had concerns about people stopping treatment with burosumab once they turn 18 because of the progressive nature of XLH and likely worsening of symptoms. But no evidence was presented on this population. The company stated that although clinical-effectiveness trial data was being collected on the continuous use of burosumab from childhood into adulthood, the clinical trial evidence informing the licence for adults with XLH was from people who started burosumab in adulthood. The committee concluded that it would evaluate burosumab for the population outlined in the company's decision problem.

Clinical effectiveness

Pivotal trial and early access programme

3.5 The pivotal clinical-effectiveness evidence for burosumab came from the CL303 trial. This was an international, phase 3, randomised, placebo-controlled trial in adults with XLH. The inclusion criteria included having serum phosphate levels below the upper limit of normal (less than 2.5 mg per decilitre), a BPI 'worst pain' score of at least 4, and a stable regimen for more than 21 days if having chronic pain medication. The trial compared burosumab with placebo for 24 weeks. After this period, people having placebo switched to burosumab. Treatment was then continued for a further 72 weeks. There were 134 people randomised (68 to burosumab; 66 to placebo) during the 24-week placebo-controlled period. Further treatment was available by entering the BUR02 open-label extension study or the second extension period of the CL303 trial. There was an interim period between these 2 studies during which 24 people had burosumab through an early access programme; the 7 remaining people had a treatment gap (mean time without treatment of 9 months). In the UK, the early access programme involved data collection from adults having burosumab free of charge (the company considers the total number to be confidential so it cannot be reported here), with data currently available for 40 people from University College London Hospitals (UCLH). Eligibility for the early access programme included the presence of debilitating symptoms including, but not limited to, pain, stiffness, and fatigue.

Trial generalisability to clinical practice

3.6 The company used the age and weight distribution of people in CL303 to inform its model (see section 3.8). The mean age was 40 years (standard deviation: 12.2 years) and the mean weight was 67.2 kg (only from people in the EU cohort). The company preferred to use data from CL303 for consistency with the efficacy and utility data used in the model. But the EAG considered that the company's early access programme, which was from the UK, better represented the expected eligible population in the NHS. People in the early access programme had a mean age of 42.8 years (standard deviation: 14.6 years) and a mean weight

of 70.3 kg. The EAG noted that people in CL303 were younger, and the weight distribution of EU cohort was lighter than in the early access programme. The clinical experts agreed that the population from the early access programme was likely to better represent the current eligible population for burosumab. During consultation, the company presented data on the average weights of people in the early access programme at various time points. The mean weights were:

- 73.6 kg, standard deviation 16.92 kg (baseline)
- 69.3 kg, standard deviation 11.64 kg (3 months)
- 72.0 kg, standard deviation 15.41 kg (6 plus or minus 3 months)
- 66.8 kg, standard deviation 10.62 kg (12 plus or minus 3 months) and
- 65.6 kg, standard deviation 13.7 kg (18 plus or minus 3 months).

The company explained that the observations showed a mean weight of less than 70 kg, because people likely lost weight with less stiffness, fatigue and improved muscle strength. So the company maintained its preference to use age and weight distributions from the CL303 trial. The EAG noted that the weight distributions from the early access programme were variable, and the mean weight at month 6 (72 kg) was similar to that at baseline (73.6 kg). Also, the patient numbers at each time point were small (133 people at baseline, 17 people at 3 months, 21 people at 6 months, 9 people at 12 months, and 10 people at 18 months). At the second committee meeting, the clinical experts explained that compared with the general population, people with XLH are generally smaller, weigh less, but have a greater BMI. They suggested that in the future, it may be reasonable to assume that the weight distribution of people with XLH who are having burosumab will fall over time. This is because they will become more active, and this will help reduce weight. Also, in the future, the population eligible for burosumab may become younger over time, and weigh less, but this is difficult to quantify. The clinical experts explained that as data on weight in the early access programme was not collected systematically, the sample sizes at the various time points were small. The committee noted that the age and weight distribution should reflect the current eligible population in the NHS. The committee considered that in the future, the age and weight distribution of the eligible population may change. But it concluded that the age and weight

distribution from the early access programme was more appropriate to use than the trial data because it better reflected the current eligible population in the NHS.

Trial outcomes

3.7 The primary outcome at 24 weeks was the proportion of people with a mean serum phosphate concentration above the lower limit of normal (2.5 mg per decilitre): 94.1% in the burosumab arm and 7.6% in the placebo arm met the primary outcome. Patient-reported outcomes including pain were measured using the BPI and WOMAC (Western Ontario and McMaster universities osteoarthritis index) questionnaires. The clinical and patient experts noted that the pain experienced by adults with XLH who take burosumab from childhood and then stop would differ from the pain experienced by someone who has lived with it for their whole life, because of ineffective conventional treatment. The EAG noted that there were potential imbalances in population characteristics between the burosumab and placebo arms at baseline. In the burosumab arm, people were older on average, had fewer fractures and worse physical function measured by WOMAC, and more people had severe pain measured by the BPI short form. The EAG noted that there was limited evidence for the clinical effectiveness of burosumab compared with placebo for patient-reported outcomes beyond 24 weeks. It noted that some of the patient-reported outcomes may be affected by a placebo effect (where the outcome improves on placebo) or regression to the mean (where the average outcome is unusually high or low at baseline and the next measure more closely reflects the true average). The committee concluded that burosumab was clinically effective at normalising serum phosphate levels, but there is uncertainty in the evidence for its effect on patient-reported outcomes such as pain.

Economic model

Company model

3.8 In its submission, the company presented a state transition cohort model to

estimate the cost effectiveness of burosumab compared with conventional care. Burosumab was modelled to improve serum phosphate levels, reduce fractures, and improve health-related quality of life through better physical functioning, reduced pain and stiffness, and fewer fractures. The model cycle was annual and included a lifetime time horizon. Morbidity (fracture rates) was dependent on the probability of serum phosphate normalisation in each treatment arm. Morbidity was not structurally linked to mortality in the model. Estimates were made on the excess mortality associated with XLH compared with the general population (see section 3.11) and an assumption was made on the extent to which burosumab may reduce this excess mortality. The committee concluded that the company's model structure was appropriate for decision making.

Stopping criteria and discontinuation

3.9 There were 2 criteria for continuing burosumab in the company's model. These were reaching a serum phosphate level above the lower limit of normal at 24 weeks and having an improvement in WOMAC total score 12 months after starting treatment. The company assumed that 16.9% of people stop burosumab treatment in year 1, based on the percentage of people in CL303 with normalised serum phosphate at week 24 and an improvement in WOMAC total score at week 48. The company assumed that 3% of people stop burosumab treatment in year 2 and subsequent years, based on clinical expert elicitation and the observed annual discontinuation rates in the early access programme. The EAG noted that the CL303 trial and early access programme did not include a stopping rule. The EAG also considered that the second criterion of improved WOMAC score may not be appropriate. This was because this measure is not commonly used in the UK and because serum phosphate normalisation may have other benefits on morbidities and mortality such as reduced opioid use. The EAG did scenario analyses without a stopping rule and assumed 7.35% discontinuation in year 1 based on the discontinuation rate at week 24 in CL303, and 3% or 0% discontinuation in year 2 and beyond. A clinical expert said that, for most people with XLH, serum phosphate would normalise at some point with burosumab, so other criteria would be used to determine whether to stop treatment. Another clinical expert explained that proposed draft guidelines (by the Rare Disease Collaborative Networks; Mohsin et al.) on burosumab included reviewing treatment yearly and considering stopping burosumab if there is no improvement

in average pain over the previous 7 days and no reduction in analgesic use. But the clinical expert added that a benefit of burosumab is increased vitality, which is not measured by a questionnaire, but means that people with XLH increase their activity up to the level of pain they had previously.

At consultation, the company provided a scenario analysis that used the BPI score as a proxy for the criteria proposed in the draft guidance from Mohsin et al. In this scenario, 65.15% of people continued burosumab. The EAG noted a greater proportion of people stopping burosumab in the scenario analysis, which may be unreasonable because of the benefits of serum normalisation on mortality and morbidity such as reduced opioid use. The EAG also noted that the mean utility change from baseline was greater for the people who met the criteria for continuing burosumab in the scenario analysis than in the base case, and there were some imbalances in baseline characteristics in CL303 (see section 3.7). The committee noted the additional benefits of burosumab, such as reduced side effects and opioid use, that adults with XLH may benefit from despite their WOMAC total score not meeting the improvement threshold.

At the second committee meeting, the clinical experts noted that reviewing treatment at 12 months may be appropriate. They explained that serum phosphate normalisation is expected, because the dose can be titrated. Therefore, the BPI score, WOMAC score, and reduction in analgesic use are reasonable considerations for stopping burosumab. But the clinical experts also agreed that a stopping rule is not needed, acknowledging that it may take time to reduce analgesic use because of dependency. The committee considered the uncertainty about the stopping criteria and noted that the early access programme did not include a stopping rule. It was unclear how a stopping rule would be implemented in clinical practice. The committee noted the different stopping criteria proposed. It considered that it was not clear which criterion to use, and a stopping rule that incorporated pain, analgesic use and physical activity would be difficult to implement in clinical practice. It noted that there is no stopping rule in burosumab's marketing authorisation, and that stopping burosumab may be associated with rapid deterioration of treatment effects (see section 3.10). So, the committee preferred not to include a stopping rule in the model.

Tapering of treatment effect

3.10 The company included assumptions around tapering of treatment effect in its model. These included assuming that it may take time to reach the maximum treatment effect after starting burosumab and that the treatment effect would decrease over time after stopping treatment. The company included different tapering assumptions for mortality and morbidity when stopping burosumab and having conventional care:

- For morbidity, 100% of the treatment effect for burosumab was applied in years 1, 2 and beyond when on treatment. Once people stopped burosumab, 50% of the treatment effect was applied in year 1 and 0% in year 2.
- For mortality, people having burosumab had 75% of the maximum treatment effect in year 1 and 100% in year 2 and beyond when on treatment. Once people stopped burosumab, the treatment effect was reduced to 75% in year 1 and 50% in year 2.

  As an alternative, the EAG assumed that the treatment tapering effect would be the same for morbidity and mortality. It assumed a 75% treatment effect applied in year 1 and 100% in year 2 and beyond, while on burosumab. Once people stopped burosumab, the treatment effect was reduced to 50% at year 1 and 0% from year 2. During the second meeting, the clinical experts confirmed that the treatment effect of burosumab would wear off after stopping treatment. This was also reported by a study by Kamenicky et al. (2023), which suggested that treatment interruption affects the treatment benefit of burosumab. The clinical experts added that in clinical practice, pausing or stopping treatment for reasons unrelated to any adverse effects (for example, pregnancy) leads to rapid deterioration in physical functioning and pain levels within a few months. The clinical experts agreed that the treatment effect in relation to morbidity would wane quickly after stopping burosumab, and the treatment effect in relation to mortality would have a longer taper. The clinical experts also considered that a 50% treatment effect reduction associated with morbidity after stopping burosumab may be optimistic. They suggested that 25% of the treatment effect for burosumab on morbidity may remain at year 1 after stopping treatment. This is because people who stop burosumab have a rapid deterioration in their condition. The committee noted the lack of evidence on the treatment effect of burosumab

in the longer term. It considered that assuming a treatment effect of 50% at year 1 after stopping burosumab may be optimistic. The committee concluded that the assumptions were arbitrary, but agreed with the EAG's approach of using the same treatment effect tapering assumptions for morbidity and mortality.

Modelling excess mortality risk from XLH

3.11 The clinical experts explained that XLH is associated with mortality. This is because of prolonged opioid use, effects on mental health, and side effects from conventional treatment including hyperparathyroidism, and long-term effects such as kidney damage. The patient experts added that the symptoms of XLH contributed to an increased risk of dying earlier. These included the increased likelihood of fractures and reduced mobility associated with fractures and pain, increased weight gain because of reduced mobility, frequent opioid use at increasing doses, and effects on mental health. The company assumed a hazard ratio of 2.88 (95% confidence interval [CI] 1.18 to 7.00) for excess mortality risk from XLH compared with the general population in the conventional care cohort. This was from Hawley et al. (2020), which used data from the UK Clinical Practice Research Datalink (CRPD) database between 1995 and 2016. The EAG preferred to use a hazard ratio of 2.33 (95% CI 1.16 to 4.67). This was from the company's confirmatory study that extended Hawley et al. and used a larger sample from the UK CRPD GOLD and CPRD AURUM databases with more recent data (from between 1995 and 2022). At the first committee meeting, a clinical expert suggested that the company's confirmatory study adjusted for socioeconomic status, which would mean that it would not account for excess mortality caused by low socioeconomic status related to XLH. The committee was not convinced that this would be the case. The committee was aware that XLH may affect a person's ability to do paid work because of both the condition itself and caring for family members, but the extent of low socioeconomic status associated with XLH and its link to mortality rates remained unclear. The committee agreed that if there was such a link, an analysis adjusting for low socioeconomic status would be preferred.

After consultation, the company did an analysis of the company's confirmatory study preferred by the EAG, using the index of multiple deprivation quintile added

as a factor covariate in a Cox proportional hazards model. From this, a hazard ratio of 2.49 (95% CI 1.23 to 5.02) was calculated. But the company preferred using the hazard ratio of 2.88 based on Hawley et al. (2020) in its base case to look at the overall impact of XLH without controlling for low socioeconomic status. The EAG had no access to the data or analysis from which the hazard ratio of 2.49 was derived, so it could not comment on the company's analysis. At the second committee meeting, the clinical experts suggested that low socioeconomic status is linked to XLH so should not be adjusted for in the analysis, but that the effects may be from childhood or adulthood. For example, struggling to get full-time employment in adulthood may be because of an impact on education during childhood not related to XLH, but could also be linked to the effects of early-onset musculoskeletal problems associated with XLH, which get worse over time because XLH is a progressive condition, and having to take time off school for surgeries. So, some effects on socioeconomic status may be associated with XLH and some may not, and mortality in people with XLH may be exacerbated by low socioeconomic status. The committee asked why the company had not chosen the HR of 2.33, which was based on a larger sample. The company explained this was because there was a reduction in the risk of mortality associated with burosumab, which was independent of socioeconomic status. The EAG highlighted the large overlapping confidence intervals of the hazard ratios across the analyses. It also noted that there may be variation by chance in studies, so it was difficult to say which estimate was more appropriate. The committee noted that socioeconomic status may modify the relationship between XLH and mortality, but the extent of this and the impact of burosumab modifying this relationship was uncertain, particularly with impacts arising from childhood. Considering the entirety of the evidence and the uncertainties in the relationship between XLH and mortality, the committee concluded that it preferred a hazard ratio of 2.33 to model the excess mortality risk from XLH compared with the general population.

Modelling mortality benefit with burosumab

3.12 The clinical trials explored by the company did not record any deaths, so the company could not use clinical trial evidence to inform assumptions on mortality in the model. It instead assumed a 50% reduction in excess mortality risk from XLH for burosumab compared with conventional care, based on clinical opinion. A

clinical expert considered that if burosumab normalised serum phosphate levels, then a reduction in mortality with burosumab was reasonable. But the clinical expert added that because the reason for mortality associated with XLH is multifactorial, and the exact cause is unknown, exploring a mortality benefit either side of 50% would be appropriate. A direct link between normalising serum phosphate levels and reducing mortality was unclear. So the EAG explored scenarios that assumed no mortality benefit with burosumab, an 11% reduction in excess mortality (from a meta-analysis of the effects of treating osteoporosis on mortality), and a 25% reduction in excess mortality. The committee agreed that a 50% reduction in excess mortality risk was an arbitrary assumption and that more evidence was needed. It considered that in the absence of evidence supporting a 50% reduction in excess mortality risk with burosumab, it was important to explore alternative scenarios. It considered that of the scenarios presented, the 11% reduction was the best available because it was based on data, although it was limited by the fact that it was based on a population with osteoporosis rather than XLH. The committee considered that evidence on the following may inform assumptions in the model:

- the relationship between XLH and the factors proposed to increase mortality risk in XLH (opioid use, effects on mental health, social deprivation, side effects of currently available treatments and consequences of reduced mobility)
- the mortality risk associated with the factors proposed to increase mortality risk
- the extent that burosumab may reduce any mortality risk.

After consultation, the company provided evidence on the multi-system effects of hypophosphataemia and factors that may increase mortality in XLH. These included:

- excess FGF23
- low phosphate levels
- obesity
- multimorbidity

- impaired mental health
- pain
- stiffness
- fatigue
- physical inactivity
- chronic opioid use
- low socioeconomic status.

The EAG commented that the potential effects of burosumab on reducing the excess mortality associated with these factors remained uncertain and were not used or quantified in the model. During consultation, a survey conducted among clinicians who manage XLH and within the Rare Disease Collaborative Network for Adult Rare Bone Diseases was submitted by a clinical expert. Collectively, the clinicians prescribed burosumab for 137 adults. There were 9 responses to the survey, which included all the centres that participated in the early access programme. In the survey, 5 out of the 9 clinical experts opted for a 25% reduction in mortality from using burosumab. At the second meeting, the clinical experts agreed that a 25% reduction in mortality was reasonable. This took into account the uncertainty of having no data on mortality, and that function may not be completely reversed, for example, because of impacts arising from childhood. The clinical experts added that multiple factors may contribute to a mortality benefit, including the direct benefits from improving serum phosphate, improvements in symptoms resulting in increased physical activity, and a significant improvement in pain that would lead to better mental health and reduced opioid use. The patient experts agreed that having burosumab leads to significant reductions in painkiller use, including opioid use. In addition, improvements in obesity and physical activity can reduce the risk of cardiovascular conditions. The clinical experts added that the mortality benefit may take time to appear, but the reduction in opioid use is usually fast. The company added that data from the early access programme at UCLH showed that 9 out of 20 people (45%) who used opioids at baseline had stopped taking opioids by year 1, and there was no new opioid use at 1 year follow up. The committee concluded that, based

on clinical opinion, it may be appropriate to model a 25% reduction in excess mortality from having burosumab, but there were uncertainties. The committee took these into account in its decision making.

Modelling excess fracture incidence

3.13 In its model, the company assumed that having normalised serum phosphate levels with burosumab resulted in a 100% reduction in excess fracture incidence rates, making the rate equal to that of the general population. The rate of fractures in the general population was based on a study by Curtis et al. (2016), which reported fracture incidence rates by age and sex in the UK between 1988 and 2012. For conventional care, excess fracture incidence was predicted from the baseline CL303 data. The EAG noted that the 100% reduction in excess fracture incidence was not based on any evidence and would likely overestimate the effect of burosumab. It did scenario analyses assuming 75% and 50% reductions in excess fracture incidence. The EAG highlighted that the Curtis et al. study reported fractures from people without XLH, whereas burosumab targets XLH-driven osteomalacia and fragility fracture incidence. The committee noted that between baseline and week 48 in CL303, there were some new fractures and pseudofractures in the burosumab and placebo arms. A clinical expert explained that it can take a long time for treatment to correct the effect of XLH on bone mineralisation. And that in the general population, fractures are usually osteoporotic or trauma fractures. But many adults with XLH have higher bone density when assessed through osteoporosis screening and so have a lower incidence of osteoporotic fractures. But they may have an increased risk of XLH-associated fractures, and in some older adults, skeletal deformities will remain, which affect the risk of fracture. The committee noted that different fracture types will cause different levels of disutility. And there may be a long-term effect because people may adapt their behaviour and activity to avoid the risk of fractures. The committee noted the high level of uncertainty in assuming a 100% reduction in excess fracture incidence rates. This was because there was a lack of data on the risk of fracture in people with XLH and normalised serum phosphate in the longer term, as well as on how people may change their behaviour if having burosumab and the effect of this on their fracture risk. The committee agreed that real-world evidence is needed to support the assumption, and exploring different morbidity benefits from a reduced excess fracture

incidence with burosumab was appropriate.

At consultation, the company maintained its preference for a 100% reduction in excess fracture incidence by referencing that 0 fractures were reported in the real-world evidence on fracture incidence for burosumab in the early access programme, as well as in the BUR02 long-term follow up and the BUR03 phase 3b single-arm study in Germany. Expert elicitation also suggested that burosumab is considered very likely to stop all future fractures (Seefried et al. 2023). The company also clarified that the fracture rate used in the model (0.024 to 0.05 by the end of the period) was greater than the estimated annual fracture rate in CL303 (0.021). The EAG highlighted the uncertainty associated with the short follow up in the CL303 trial, and added that bone normalisation may take months or years based on the European Medicines Agency assessment report. The clinical experts emphasised that the bones of people with XLH are different to bones in people with other conditions such as osteoporosis, so standard osteoporotic-type fractures will likely be less frequent. The clinical expert survey submitted by 1 of the clinical experts during consultation (see section 3.12) noted that in XLH, bones are often wider and have greater bone density. Out of 8 clinical experts, 4 predicted that burosumab would reduce excess fracture incidence to the general population level, 3 predicted it would reduce it to below the general population level, and 1 predicted it would be above the general population level.

During the second committee meeting, the clinical experts explained that fractures can be multifactorial in origin, and repairing the bone mineralisation aspect of XLH would lead to a reduction in a factor related to fracture incidence and result in fewer fractures over time. In addition, improved muscle strength and reduced opioid use may reduce the risk of falls, and therefore fractures. The patient experts also highlighted the increased confidence when walking, feeling stronger, and having less worry about fractures when moving. The committee agreed that there was significant uncertainty about how much the excess incident fracture rate would reduce with burosumab, particularly assuming a 100% reduction in excess fracture incidence. It noted the short follow-up periods of the studies, that improvements in bone mineralisation may take time, and that factors such as behavioural changes may affect the subsequent fracture risk. It concluded that assuming a 100% reduction in excess incident fractures may be appropriate, but that this was highly uncertain. The committee took this into

account in its decision making.

Health-related quality of life

Source of utility values

3.14 CL303 did not collect EQ-5D data, which is the preferred measure of health-related quality of life in the NICE reference case. The company used WOMAC index scores from CL303 and BUR02 and mapped these to the EQ-5D using the Wailoo et al. (2014) mapping algorithm. To extrapolate short-term data from the trials, the company fitted a non-linear asymptotic model using data from people originally randomised in CL303 to the burosumab and conventional care arms independently. This was to predict the change in utility beyond the observed period. The company explained that because of the way the trials were set up, data was collected at various time points. For the placebo arm there was data to 24 weeks, and for burosumab there was data from the 24-week randomised controlled CL303 trial, the CL303 extension up to week 96, and the further open-label extension study BUR02. The company added that XLH is a rare condition, so any evidence on long-term impact is important to capture. The EAG had concerns that the data included in the asymptotic model after week 96 was from a smaller number of people than the data up to week 96, included data from subsets of the original randomised population, included US-only data at some time points, and had increased variability in results. The EAG stated that the data after 96 weeks had a large impact on the modelled results. It explained that at week 96 in the asymptotic model, the modelled utility lay above the observed utility for the burosumab arm, which was then extrapolated over the lifetime time horizon of the economic model. The company highlighted that the predicted utilities in the model were within the 95% confidence interval predicted by the model, including at week 96. The clinical expert submission noted that there may be a cumulative benefit of burosumab over time. The committee acknowledged that the low number of people informing the asymptotic model after week 96 added uncertainty in the extrapolations. Also, some data beyond week 96 was from the US only, and a spike in utility was observed at this point. The committee valued including extra data on a rare condition such as XLH. So it suggested that the company explore:

- fitting a hierarchical model
- smoothing the data beyond week 96
- both a hierarchical model and smoothing the data beyond week 96.

The company could not develop the suggested models in the timeframe of consultation. It explained that its asymptotic model inherently smoothed the observed curve and avoided extrapolating trends observed within the trial period over the extended period. Also, it was unclear if a higher parametrised model would increase clarity because of the limited empirical data and scope for elicitation in a rare condition like XLH. At the second meeting, the company highlighted that the post-96-week data was important because it included people originally enrolled in CL303, and that the people in the trial from the US were separated from the European cohort because of administration reasons with the license. The EAG commented that the company provided no new evidence or information to support its argument. The committee concluded that in the absence of any other scenarios, it preferred the EAG's approach.

Adjusting utilities for placebo effect

3.15 The company used non-placebo-adjusted utility values in its model. This meant that the placebo effect observed in the 24-week placebo-controlled period of CL303 was not deducted from the mean change from baseline utility for the burosumab arm. Utility values showed an initial improvement at 12 weeks in the placebo arm of CL303. The company argued that utilities are multifactorial and any placebo effect on utility is short-lived. This is because the utility returned to near baseline levels by week 24, and this effect was seen in the CL303 placebo arm for all the patient-reported outcomes. The committee agreed that the potential placebo effect observed at week 12 in CL303 seemed to diminish at week 24, although this did not return to the baseline value exactly. The EAG acknowledged the limited 24-week placebo-controlled trial period but highlighted that not adjusting the utilities for placebo effects adds important uncertainty. Also, that the cost-effectiveness results were very sensitive to the utility values, so any small placebo effect could have a large impact on the cost effectiveness

of burosumab. The EAG did a scenario analysis using placebo-adjusted utility values to explore this uncertainty. It explained that the placebo-adjusted utility values were not in its base case because there was only comparative data with placebo up to week 24, whereas for burosumab there was data up to week 96 (and beyond; see section 3.14). So the small effect was extrapolated based on data up to week 24. The committee had concerns about whether the analyses presented would reflect clinical practice, because different issues may underlie regression to the mean in clinical practice. The clinical expert highlighted that there was no apparent regression to the mean for outcomes related to function. They noted that as function improved, pain did not improve as much, so there may be factors explaining the results other than a placebo effect. But the committee noted that a regression to the mean was possible, because people usually enter trials when their symptoms are worse. It considered that the 7-day wash-up period at the beginning of the CL303 trial for people on conventional treatment may not have been enough time to avoid a regression to the mean effect. The committee agreed that it is best practice to take into account data from the placebo arm of clinical trials. So it concluded that the EAG scenario using placebo-adjusted utility values was appropriate.

Disutility for incident fractures

3.16 In its model, the company applied a disutility for incident fractures that continued over the lifetime of the model. This was for fractures to the tibia, fibula, femur, pelvis, foot, or spinal vertebrae. All other fractures had a utility decrement in the first year only. The company argued that fractures in XLH are slow healing and some untreated fractures do not heal. And that impaired bone mineralisation in XLH may mean that fractures can have a long-term impact on health-related quality of life. The EAG acknowledged that some fractures may accrue a lifetime utility decrement, such as fractures to the tibia, fibula, femur, pelvis, foot or spinal vertebrae. But the EAG had concerns that the disutility may be overestimated, because there is potential for an improvement in health-related quality of life for other fractures healing over time. The EAG highlighted that mortality and morbidity were modelled independently and the lifetime disutility for incident fractures did not adjust for fracture-specific mortality. So, there was potential for double counting the morbidity effects because the utility values extrapolated over time were treatment specific, and the EAG considered that the morbidity

effects were already captured. The EAG did a scenario analysis in which the disutility of incident fractures was applied in the first year only. The committee acknowledged the high uncertainty with assuming a lifetime disutility for incident fractures in the model. It agreed that it was appropriate to include a disutility for incident fractures, but that the duration of disutility in the model would vary depending on the type of fracture included. It would also welcome more information on the length of time that fractures in different bones would affect quality of life.

At consultation, the company did an evidence search to show the prolonged health-related quality-of-life impacts from various bone fractures and the differences in fracture sites in people with osteoporosis or people at risk of fragility fractures. The EAG agreed that 1 of the 3 studies provided by the company was relevant to address the committee's concerns on the length of time that fractures in different bones would affect quality of life (see section 3.17). This study suggested that hip fractures can have negative long-term effects on health-related quality of life. It also reported that fractures that happened closer to follow-up assessments were associated with more significant impacts on health-related quality of life compared with fractures that happen a long time before the follow-up assessment. So the EAG suggested that a lifetime disutility assumption may not be appropriate. During the second committee meeting, the clinical expert explained that it is usual for adults to have pseudofractures that do not heal for many years despite conventional treatment. The committee noted that the surveyed clinical experts estimated that the median proportions of adults with XLH with a recently diagnosed symptomatic pseudofracture who were likely to remain symptomatic or have a lower quality of life with conventional treatment were:

- 80% at 1 year
- 50% at 2 years
- 25% at 5 years
- 10% lifelong.

During the second meeting, the committee noted that disutility may vary based on fracture type but that these estimates were not factored into the model. It noted that the company's approach may be appropriate, but there

were uncertainties. After the second committee meeting, the company provided scenario analyses applying the corresponding disutility values suggested by the clinical expert survey at 1 year, 2 years, 5 years, and lifelong time points. The committee concluded that this approach of corresponding disutility for incident fracture to clinical expert survey was preferred.

Utility benefit for carers and family members

3.17 The company assumed a spillover utility benefit for informal carers or family members in its model. This was 20% of the utility benefit for people with XLH who had burosumab, based on a health-related quality-of-life research study of 19 people with XLH that also included carers with XLH. The spillover utility benefit was applied to 2 informal carers or family members. At the first committee meeting the company clarified that the utility benefit was split between the 2 informal carers so that in total the benefit was 20% rather than 40%. The company highlighted that the quality of life of informal carers and family members can be affected by being depended on, having increased responsibilities, and restrictions in taking part in family activities. As XLH improves, people with XLH may be able to do more daily tasks, reducing the caring responsibilities, so the company assumed a spillover benefit. The EAG included a utility benefit for 1 informal carer or family member only. A clinical expert submission noted that because XLH is a progressive condition, there is a progressive carer burden over time as the impact of XLH increases. A patient expert explained that within a family, people without XLH or those with milder symptoms of XLH may work together to look after those with more severe XLH. Also, some people may have to look after multiple family members with XLH. The patient expert added that as someone with XLH reaches older age, external carer support may be needed in addition to family support. The committee acknowledged the need for carers' support for adults with XLH. It also considered that support from family members or informal carers for each adult would vary. The committee considered that the company's research study consisted of a small sample and included carers with XLH. It noted that the utility benefit could be double counted if the carer had XLH and was having burosumab themselves, also noting the EAG's comment that if data from people with XLH was excluded from the company's research study there was limited evidence for a utility benefit for carers. The EAG added that

because of the limited treatment options, family members with XLH are likely to also be considered eligible for burosumab. The committee agreed that the following uncertainties need to be further addressed:

- the average number of carers an adult with XLH would have
- the impact of caring for an adult with XLH on quality of life
- how burosumab would affect the quality of life of carers.

The committee suggested that any exploration of the potential benefit of burosumab on carer utility should only include carers without XLH, to avoid potentially double counting the utility benefits of burosumab.

During consultation, a patient organisation provided a survey on the impact on carers in XLH. In this survey, out of 24 carers, 3 reported no change in wellbeing after burosumab, 2 had a moderate improvement, and 19 had a significant improvement. After burosumab, the average total carer hours per week decreased by 61% (19 to 7.5 hours per week). Among adults with XLH not taking burosumab (n=46), 16 reported needing 0 carers, 10 reported needing 1 carer, and 18 reported needing 2 or more carers. In the 24 people needing at least 1 carer, after burosumab 9 did not need a carer anymore, 10 had 1 carer, and 5 had 2 or more carers. The patient experts described a large impact on informal carers and family members. This included carers with XLH, because those with a milder condition help those with more severe symptoms, and this can have both physical and mental impacts. Also, people with XLH can be highly dependent on their informal carer or family member, including for transportation, attending appointments, and daily tasks. The company highlighted that XLH is heterogenous in its presentation, and people eligible for burosumab are those who would have more severe symptoms. The committee noted that in previous NICE evaluations, more than 1 carer was only considered for conditions for which 24-hour care was needed. It agreed that, based on all of the evidence provided, it preferred the EAG's approach of including carer utility benefit for 1 carer. But it noted that there were uncertainties because this assumption may overestimate carer utility benefit associated with burosumab.

Cost effectiveness

Acceptable ICER

3.18 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty in the evidence and modelling, specifically:

- burosumab's effect on patient-reported outcomes such as pain (see section 3.7)
- the excess mortality risk associated with XLH (see section 3.11)
- the extent to which burosumab affects the relationship between socioeconomic status and mortality (see section 3.11)
- the extent to which burosumab reduces excess mortality risk (see section 3.12)
- the short follow up of trials and assumption of a 100% reduction in excess fracture incidence (see section 3.13)
- the extrapolations involving small numbers of people informing the asymptotic model after week 96 and potential placebo effects (see sections 3.14 and 3.15)
- the assumption of a lifetime disutility for some types of incident fractures (see section 3.16)
- the assumption of a utility benefit for carers and family members (see section 3.17).

Taking into account the uncertainties, the committee concluded that an

acceptable ICER would be around the middle of the range NICE considers an effective use of NHS resources (£20,000 to £30,000 per QALY gained).

The committee's preferred assumptions

3.19 The committee's preferred assumptions were:

- using the age and weight distribution from the early access programme (see section 3.6)
- not applying a stopping rule for burosumab (see section 3.9)
- applying a 2.33 hazard ratio to estimate the excess mortality risk from XLH compared with the general population (see section 3.11)
- applying a 25% reduction in excess mortality risk with burosumab (see section 3.12)
- applying the same treatment effect tapering assumptions for modelled morbidity and mortality (see section 3.10)
- assuming a 100% reduction in excess incident fractures, equal to that of the general population (see section 3.13)
- excluding data beyond week 96 in the model for extrapolating utility values (see section 3.14)
- adjusting for the placebo effect in the model when extrapolating utility values (see section 3.15)
- varying duration of disutility for fractures depending on the type of fracture to correspond with the clinical expert survey (see section 3.16)
- applying a carer utility benefit of burosumab to 1 carer (see section 3.17).

The ICER when applying the committee's preferred assumptions was around the middle of the range normally considered an acceptable use of NHS resources (£20,000 to £30,000 per QALY gained). The exact ICERs are confidential and cannot be reported here.

Other factors

Equality

3.20 The patient and clinical experts explained that some people with XLH may have an increased likelihood of having lower socioeconomic status than the general population (see section 3.2 and section 3.11). This is because XLH affects the ability of people with XLH and their carers across generations to do paid work. The committee also considered potential discrimination based on age, geographical disparity, or sex. Because its recommendation does not restrict access to treatment for some people over others, the committee agreed these were not equality issues.

Uncaptured benefits

3.21 The committee recognised that burosumab is the first treatment that inhibits the action of excess FGF23, and so affects the pathophysiology of XLH. It also considered comments from clinical and patient experts that administration of burosumab is less burdensome than that of conventional treatment (see section 3.3). The committee did not identify any additional benefits of burosumab that were not captured in the economic modelling. So, it concluded that all additional benefits of burosumab had already been taken into account.

Severity

3.22 The company explored whether burosumab met NICE's criteria for a severity modifier to be applied. It calculated the absolute and proportionate QALY shortfall for people with XLH having conventional care compared with people without XLH. The company presented 2 sets of estimates. The first assumed all people started treatment at 18 years to reflect that the evaluation is considering burosumab for an adult population. The second assumed a starting age that reflected CL303 (average age of 40). The EAG also provided an estimate based on the population having burosumab through the early access programme in England and its preferred estimate of excess mortality risk associated with XLH.

The NICE health technology evaluations manual states that absolute and proportional shortfall calculations should include an estimate of the total QALYs for the general population with the same age and sex distribution as those with the condition. The company and EAG estimates based on the distributions of people having treatment in CL303 and on the early access programme were below 0.85 for the proportional QALY shortfall and below 12 for the absolute QALY shortfall. So burosumab did not meet the criteria for severity weighting to be applied.

Conclusion

Recommendation

3.23 The clinical evidence suggested that burosumab improved key outcomes in people with XLH. The committee concluded that the ICER resulting from its preferred assumptions was within the range that NICE considers an acceptable use of NHS resources. So, burosumab is recommended for routine commissioning.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has X-linked hypophosphataemia and the healthcare professional responsible for their care thinks that burosumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Baljit Singh
Vice Chair, technology appraisal committee B

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Summaya Mohammad
Technical lead

Yelan Guo, Mary Hughes
Technical advisers

Vonda Murray
Project manager

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