NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance

Burosumab for treating X-linked hypophosphataemia in adults

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using burosumab in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: November 2023

Note that this document is not NICE's final guidance on burosumab. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using burosumab in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 3 January 2024
- Second evaluation committee meeting: 15 February 2024
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Burosumab is not recommended, within its marketing authorisation, for treating X-linked hypophosphataemia (XLH) in adults.

1.2 This recommendation is not intended to affect treatment with burosumab that was started in the NHS before this guidance was published. Adults having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Usual treatment for XLH 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. This 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.

There are uncertainties in the assumptions used in the economic model, particularly about the long-term effects of burosumab on how long people live, fracture rates and the quality of life of people with XLH and their carers. And all of the cost-effectiveness estimates are above the range normally considered an acceptable use of NHS resources. So, burosumab is not 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 and it would have also applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

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. 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 in attempt 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 social deprivation 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 including diarrhoea, which substantially affects people's ability to do day to day activities, and hyperparathyroidism, which can cause permanent kidney damage. Taking oral phosphate also has other difficulties, 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 for some people, conventional treatment is tolerated. 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. However, the committee noted no evidence was presented on this. The company stated that although clinical-effectiveness clinical 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

Trial design

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. There was an interim period during which most people had burosumab through an early access programme, otherwise they had a treatment gap. Further treatment was available by entering the BUR02 open-label extension study or the second extension period of the CL303 trial.

Trial generalisability to clinical practice

3.6 The company used the age and weight distribution of people in CL303 (see section 3.8) to inform its model. 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 represents the expected eligible population in NHS clinical practice. This is because 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 is likely to better represent the current eligible population for burosumab. The committee concluded that using the age and weight distribution from the early access programme is more appropriate than the trial because it better reflects the eligible population in NHS clinical practice.

Normalising serum phosphate levels

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 were measured using the BPI and WOMAC (Western Ontario and McMaster universities osteoarthritis index) questionnaires. The EAG noted that there were potential imbalances between the burosumab and placebo arm 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 clinical effectiveness of burosumab on patient-reported outcomes beyond 24 weeks compared with placebo. 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 clinical and patient experts noted that pain experienced by adults with XLH who stop burosumab treatment from childhood would differ to pain experienced by someone who has lived with it for their whole life because of ineffective conventional treatment. The committee concluded that burosumab was clinically effective at normalising serum phosphate levels.

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. This was achieving 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. Therefore, the company assumed that 16.9% of people discontinue burosumab 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 discontinue burosumab in year 2 and subsequent years, and this was 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 is because it 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 burosumab. Another clinical expert explained that the proposed draft guidelines (by the Rare Disease Collaborative Networks) on burosumab include reviewing treatment annually and considering stopping burosumab if there is no improvement in the average pain over the last 7 days and no reduction in analgesic use. However, 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. The committee considered uncertainty on the stopping criteria and noted that the early access programme does not include a stopping rule. It noted that it was unclear how a stopping rule would be implemented in clinical practice. The committee also 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. Therefore, 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 burosumab. 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 and 2. 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. Once people stopped burosumab, the treatment effect was reduced to 75% in year 1 and 50% in year 2.

Alternatively, the EAG assumed the same treatment tapering effect on morbidity and mortality and applied the company's mortality tapering assumptions to both. The committee concluded that the assumptions were arbitrary but agreed with the EAG's approach to using the same assumptions for both morbidity and mortality treatment effect tapering.

Modelling excess mortality risk from XLH

3.11 The clinical experts explained that XLH is associated with mortality because of prolonged opioid use, effects on mental health, and side effects from conventional treatment which include hyperparathyroidism and long-term effects such as kidney damage. The patient experts added that the symptoms of XLH contribute to an increased risk of dying earlier. These include 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 used Hawley et al. but also used a larger sample from the UK CRPD GOLD and CPRD AURUM databases with more recent data between 1995 and 2022. A clinical expert suggested that the company's confirmatory study adjusted for deprivation, which would mean that it would not account for excess mortality caused by deprivation 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, however the extent of social deprivation associated with XLH and its link to mortality rates remained unclear. The committee agreed that if such a link did exist, an analysis adjusting for deprivation would be preferred. The committee concluded that it preferred a larger sample with more recent data, as seen in the company's confirmatory study, to estimate excess mortality associated with XLH. It therefore 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, therefore the company could not use clinical trial evidence to inform assumptions on mortality in the model. The company 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 has an impact on normalising serum phosphate levels, then a reduction in mortality with burosumab is reasonable. However, 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% is appropriate. The committee noted that the direct link between normalising serum phosphate levels and reducing mortality is unclear. 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 25% reduction in excess mortality. The committee considered that in the absence of evidence supporting a 50% reduction in excess mortality risk with burosumab, alternative scenarios were important to explore. It stated that of the scenarios presented, the 11% reduction was the best available because it was based on data, although limited by the fact it was based on a population with osteoporosis rather than XLH. The committee suggested 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 factors proposed to increase mortality risk
- the extent that burosumab may reduce any mortality risk.

The committee agreed that a 50% reduction in excess mortality risk is an arbitrary assumption. The committee concluded that more evidence, either direct or indirect, is needed, but in the absence of more compelling evidence it is likely that the reduction in excess mortality risk with burosumab is below 50%.

Modelling excess fracture incidence

3.13 In its model, the company assumed that having normalised serum phosphate levels with burosumab results in a 100% reduction in excess fracture incidence rates, equal to the general population. The rate of fractures in the general population was based on a study from 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 will likely overestimate the effect of burosumab. It did scenario analyses assuming a 75% and 50% reduction 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 the effect of XLH on bone mineralisation can take a long time to be corrected by treatment. Also, that in the general population, fractures are predominantly expected to be osteoporotic fractures or trauma fractures. However, many adults with XLH have higher bone density when assessed through osteoporosis screening and therefore 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 have different levels of disutility. Also, 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 long-term fracture rates for people with XLH with normalised serum phosphate, as well as how people may change their behaviour if having burosumab and the effect of this on their fracture risk. The committee concluded that real-world evidence is needed to support the assumption and exploring different morbidity benefits from a reduction in excess fracture incidence with burosumab is appropriate.

Health-related quality of life

Source of utility values

3.14 CL303 did not measure EuroQol-5D (EQ-5D), which is the preferred measure of health-related quality of life in the NICE reference case. The

company used WOMAC 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 over the longer term, the company fitted a non-linear asymptotic model using data from people originally randomised in CL303 to the burosumab and conventional care arm 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, there were various data collection timepoints. 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, included data from subsets of the original randomised population, including US-only data at some timepoints, and had increased variability in results. The EAG stated that the data after 96 weeks had a large impact on the modelled results. The EAG explained that at week 96 in the asymptotic model, the modelled utility lies above the observed utility for the burosumab arm, which is 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 the low number of people informing the asymptotic model after week 96 adds 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 agreed that in the absence of any other scenarios, it preferred the EAG's approach. However, the committee valued including extra data on a rare condition such as XLH. So it suggested that the company

explore fitting a hierarchical model, a smoother on the data beyond week 96, or both.

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. The committee noted that 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 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 are very sensitive to the utility values, so any small placebo effect can 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. 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 exactly baseline value. The committee concluded that it is best practice to take into account data from the placebo arm of clinical trials. The committee therefore 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. The company argued that fractures in XLH are slow healing and some untreated fractures do not heal. Also, 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. However, 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 are modelled independently and the lifetime disutility for incident fractures does not adjust for fracture-specific mortality. So, there is a potential of double-counting the morbidity effects because the utility values extrapolated over time are treatment-specific and the EAG considered the morbidity effects were already captured. The EAG explored a scenario analysis in which the disutility of incident fractures is applied in the first year only. The committee acknowledged the high uncertainty with assuming a lifetime disutility for incident fractures in the model. It concluded that a disutility for incident fractures is appropriate to include but the duration of disutility in the model would vary depending on the type of fracture included. It further concluded that it would welcome more information on the length of time that fractures in different bones would affect quality of life.

Utility benefit for carers and family members

3.17 The company assumed a spillover utility benefit for 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 carers or family members. At the committee meeting the company clarified that the utility benefit was split between the 2 carers so that in total the benefit was 20% rather than 40%. The company highlighted that the quality of life of 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, therefore the company assumed a spillover benefit. The EAG included a utility benefit for 1 carer or family member only. A clinal 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 who have milder symptoms of XLH may work together to look after those with a more severe form of 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 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, 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 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. The committee agreed that, based on the evidence currently provided, it preferred the EAG's assumption to only include carer utility benefit for 1 carer. But, it noted that this assumption may overestimate carer utility benefit associated with burosumab.

Cost-effectiveness estimates

3.18 The committee's preferred assumptions included:

- 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 the same treatment effect tapering assumptions for modelled morbidity and mortality (see section 3.10)
- including data beyond week 96 in the model for extrapolating utility values, but using a hierarchical model or smoother effect on the data (or both) to account for the low population numbers and data from different subpopulations from the CL303 extension studies (see section 3.14)
- adjusting for placebo effect in the model for extrapolating utility values in the absence of evidence supporting that the placebo effect is not maintained beyond the trial period (see section 3.15)
- applying a carer utility benefit of burosumab to 1 carer (see section 3.17).

The committee noted that, for a single technology evaluation, the standard incremental cost-effectiveness ratio (ICER) range that represents an effective use of NHS resources is £20,000 to £30,000 per quality-adjusted life year (QALY) gained. The company's base-case ICER for burosumab was substantially above £100,000 per QALY gained. Applying the committee's preferred assumptions further increased the ICER.

The committee noted that uncertainty remained around the following:

- the effect of burosumab on the excess mortality risk associated with burosumab, which it expected to be lower than the 50% reduction modelled by the company (see section 3.12)
- the effect of serum phosphate normalisation on reducing new fractures in people with XLH and whether people with normal serum phosphate would have the same number of fractures as the general population. It

expected that this may be overestimated in the company model (see section 3.13)

- the duration of disutility for fractures in the model and whether this may vary depending on the type of fracture included. The committee considered that the company's assumption of lifelong duration of disutility may be an overestimate in the company model (see section 3.16)
- the number of carers an adult with XLH would have, the extent to which caring for people with XLH affects quality of life, and how caring for people who are having burosumab impacts quality of life. The committee considered that the company assumptions may overestimate the benefit of burosumab on carer quality of life (see section 3.17).

The committee considered that it needed more information to address these uncertainties. The committee noted that some of these uncertainties are related to the rarity of the condition and how this affects evidence generation. When taking into account the committee's preferred assumptions, the most likely ICER for burosumab was substantially above £30,000 per QALY gained.

Other factors

Equality

3.19 Patient and clinical experts explained that some people with XLH may have an increased likelihood of having higher levels of social deprivation 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. Because its recommendation does not restrict access to treatment for some people over others, the committee agreed this was not an equality issue.

Severity

3.20 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 had a starting age of 18 to reflect that the evaluation is considering burosumab for an adult population. The second assumed a starting age which 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 either the distribution of people having treatment in CL303 or the early access programme were below 0.85 for proportional QALY shortfall and below 12 for absolute QALY shortfall. Therefore, burosumab did not meet the criteria for severity weighting to be applied to the QALYs.

Conclusion

Recommendation

3.21 The committee's preferred cost-effectiveness estimates for burosumab were above the range that NICE considers an acceptable use of NHS resources. So, the committee concluded that it could not recommend burosumab for treating XLH in adults.

4 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

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

Mary Hughes

Technical adviser

Vonda Murray

Project manager

ISBN: [to be added at publication]