NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Evaluation consultation document

Burosumab for treating X-linked hypophosphataemia in children and young people

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 context of national commissioning by NHS England. The highly specialised technologies evaluation committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts, patient experts and NHS England.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the committee. NICE invites comments from the consultees and commentators 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 the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance on the use of burosumab in the context of national commissioning by NHS England?
- 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: June 2018

Note that this document is not NICE's final guidance on this technology. 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 consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final evaluation determination.
- Subject to any appeal by consultees, the final evaluation document may be used as the basis for NICE's guidance on using burosumab in the context of national commissioning by NHS England.

For further details, see the interim process and methods of the highly specialised technologies programme.

The key dates for this evaluation are:

Closing date for comments: 6 July 2018

Second evaluation committee meeting: 25 July 2018

Details of membership of the evaluation committee are given in section 6.

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

1 Recommendations

1.1 Burosumab is not recommended, within its marketing authorisation, for treating X-linked hypophosphataemia (XLH) with radiographic evidence of bone disease in children aged 1 year and over, and in young people with growing skeletons.

1.2 This recommendation is not intended to affect treatment with burosumab that was started in the NHS before this guidance was published. Children and young people 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. This decision should be made jointly by the clinician and the child or young person, and their parents or carers.

Why the committee made these recommendations

XLH is a genetic condition that causes significant skeletal deformities in children from a young age, and lifelong disability and pain. Conventional therapy consists of managing symptoms and disability, and supplements of oral phosphate and active vitamin D (such as alfacalcidol). Oral phosphate has a complex dosing regimen, unpleasant taste and side effects.

Evidence from clinical trials suggests that burosumab provides short-term clinical benefits in children aged between 1 and 12 years, but the evidence is limited and uncertain, and there is no evidence in young people between 13 and 17 years.

It is expected that there is some lifetime benefit for people treated with burosumab because it can prevent irreversible bone damage. However, the long-term consequences of the progressive bone disease and ongoing metabolic symptoms of XLH, which would not be affected by burosumab, are uncertain.

The cost-effectiveness estimates for burosumab are all much higher than the range NICE normally considers acceptable for highly specialised technologies. Therefore, burosumab does not appear to provide value for money within the context of a highly specialised service, and is not recommended for use in the NHS.

2 The condition

2.1 X-linked hypophosphataemia (XLH) is a rare, genetic, chronically debilitating and deforming condition. It is an X-linked dominant disorder 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.

2.2 Because XLH is a genetic condition, it often affects several members of a family. Skeletal abnormalities such as bowed or bent legs, below average height and irregular growth of the skull are early signs of XLH. Children may also present with delayed walking or waddling gait. Bone defects are common in children with XLH, and can cause pain and subsequently limit physical functioning. When bone growth stops, bone deformities become irreversible. Other manifestations of XLH include dental problems and hearing loss. Adults with XLH can have symptoms such as osteomalacia (causing an increased risk of bone fractures and other complications), muscle weakness, pain and fatigue.

2.3 The aim of current treatment is to improve growth, decrease morbidity, prevent skeletal deformities and reduce pain. For most people with XLH, clinical management consists of vitamin D supplementation and oral phosphate (often with dosing 4 to 6 times a day). People with XLH often need orthopaedic surgery to correct bone deformities.

3 The technology

3.1 Burosumab (Crysvita, Kyowa Kirin) is monoclonal antibody that binds to and inhibits the activity of FGF23. By inhibiting FGF23, burosumab is expected to increase reabsorption of phosphate from the kidney and, through vitamin D production, improve intestinal absorption of calcium and phosphate. Burosumab has a conditional marketing authorisation for 'the treatment of X-linked hypophosphataemia with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons'.

3.2 Burosumab is administered via subcutaneous injection once every 2 weeks. The recommended starting dose is 0.4 mg/kg, the normal maintenance dose is 0.8 mg/kg and the maximum dose is 2 mg/kg up to 90 mg. Doses should be rounded to the nearest 10 mg. Treatment can begin in children aged 1 year and can continue until the skeleton stops growing.

3.3 The adverse reactions listed as very common (that is, occurring in 1 in 10 people or more) in the summary of product characteristics for burosumab include: injection site reactions, headache, pain in the extremities, decreased vitamin D, rash, toothache, tooth abscesses, myalgia and dizziness. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.4 The list price of burosumab in England is £2,992 (excluding VAT) per 10 mg vial (company submission).

4 Consideration of the evidence

The evaluation committee (see section 6) considered evidence submitted by Kyowa Kirin, the views of people with the condition, those who represent them and clinical experts, NHS England and a review by the evidence review group (ERG). See the committee papers for full details of the evidence. In forming the recommendations, the committee took into account the full range of factors that might affect its decision, including in particular the nature of the condition, the clinical effectiveness, value for money and the impact beyond direct health benefits.

Nature of the condition

Course of XLH

4.1 The symptoms of X-linked hypophosphataemia (XLH) usually start in early childhood. The clinical experts highlighted that XLH is heterogeneous, meaning that people with the condition can have a variety of symptoms of different severities, and that symptoms may start later in life. The clinical experts also noted that XLH leads to bone-related and non-bone-related manifestations. The symptoms of XLH in children can include bone defects, pain, functional impairment, fatigue, dental problems and, in some people, hearing loss. The committee heard that children with XLH are often unable to participate in educational and social activities, which has a substantial emotional impact on the child and their family. It recognised that bone defects will become permanent if the condition is untreated while the skeleton is growing. This can result in skeletal abnormalities continuing into adulthood, and lifelong disability and pain. The clinical experts explained that there can also be progressive bone disease in adults, including osteomalacia and accompanying stress fractures, pain and disability. The committee acknowledged that some manifestations of XLH will continue after the skeleton matures. The clinical experts noted that the metabolic manifestations of XLH that occur

in children, such as fatigue and muscle weakness, also occur in adults. The committee agreed that, in the absence of evidence, it was not possible to determine the relative importance of pre-existing skeletal deformities, and ongoing bone and metabolic manifestations in adults. It recognised that XLH affects people from a young age and continues to affect them into adulthood.

Treatment pathway

4.2 The patient experts noted that conventional therapy (vitamin D and phosphate) must be taken 4 to 6 times a day, which interferes with usual activities (school or work). This treatment can also disturb sleep because of night-time doses (although these are not always used). The clinical experts agreed that impractical dosing regimens, and an unpleasant taste and side effects, contributed to poor adherence to this therapy (see section 4.14), and the committee recognised that this was an issue. The patient experts explained that, even when children have with vitamin D and phosphate from a young age, severe skeletal deformities can still occur. Surgical intervention is often needed to correct skeletal deformities. The committee concluded that there is an important unmet need for an effective and practical treatment for XLH.

4.3 The patient and clinical experts explained that the earlier treatment is started the better the outcomes. The committee recalled that skeletal deformities would continue into later life if untreated in childhood (see section 4.1). The clinical experts explained that they aim to start treatment as early as possible, and delays in starting treatment can increase the need for corrective surgery. The committee accepted that starting treatment for XLH early was likely to be beneficial.

4.4 The committee understood that currently all children and young people with XLH are offered conventional therapy. However, the committee recalled that XLH is heterogeneous both in symptoms and severity, and in its response to treatment (either vitamin D and phosphate, or new

treatments such as burosumab). The clinical and patient experts highlighted that, if recommended, they would expect to consider burosumab for all people with XLH. The clinical experts noted that it is not possible to predict how well the condition will respond to treatment. The committee recognised that, because XLH is a heterogeneous condition, it is challenging to understand who will benefit most from treatment. It concluded that, given the evidence presented, it was not able to identify any subgroups that would benefit more from treatment or that should be considered separately.

4.5 The committee recalled that skeletal deformities can continue into adulthood in people who had been taking conventional therapy from a young age (see section 4.2). The clinical experts noted that people are given the opportunity to stop conventional therapy when bone growth stops. A patient expert explained that, in this situation, people make the choice between continuing the treatment and having unpleasant side effects, or living with symptoms. They noted that some people with XLH can manage without the treatment after childhood but, for some people, the benefit of treatment outweighs the unpleasant side effects. The committee recognised that XLH is a heterogeneous condition and whether someone chooses to continue conventional therapy in adulthood is an individual decision. The clinical experts suggested that there may be some benefit to continuing treatment into adulthood, and noted that some people who stop treatment will start again when symptoms returns. The committee acknowledged this, but noted that the marketing authorisation for burosumab does not include adults. The committee agreed that it was unable to consider burosumab in adults because this is outside its marketing authorisation. It concluded that burosumab could be considered for use in children and young people.

Impact of the new technology

Patient and clinician perspectives

4.6 One parent recalled that their child had struggled emotionally and physically when having conventional therapy. They explained that there had been significant improvements in their child's symptoms, emotional state, independence and involvement in sporting activities and social events since starting treatment with burosumab. The clinical experts explained that it is challenging to heal bone defects with conventional therapy, and only a few people are expected to have improvements with conventional therapy, but that burosumab is expected to provide significant bone healing. The clinical experts also explained that one of the main benefits with burosumab is the improved convenience of dosing compared with conventional therapy. The committee recalled that the complex dosing regimen of conventional therapy made it highly challenging (see section 4.2). It concluded that, based on the patient and clinical experts' experiences, burosumab could provide substantial benefits to people with XLH, including improved convenience.

Clinical studies

4.7 The main sources of clinical evidence submitted by the company came from 3 studies:

- CL205: an ongoing multicentre single-arm study including 13 children aged 1 to 4 years with XLH
- CL201: an ongoing multicentre open-label dose-finding study including 52 children aged 5 to 12 years with XLH, in which they were randomised to have burosumab either monthly or bi-weekly (26 people had burosumab bi-weekly, consistent with the marketing authorisation)
- CL002: a retrospective natural history study in people aged 5 to 12 years who have had treatment with conventional therapy.

The ERG explained that there was an imbalance in baseline disease severity between CL201 and CL002 because of important differences in the inclusion criteria. The committee understood that this could be associated with differences in treatment effect, and agreed that it should be taken into account when interpreting the clinical-effectiveness results. It discussed the generalisability of the burosumab studies to the XLH population in England, and noted that only people with a Rickets Severity Score (RSS) of 1.5 or above could be included in the studies. The committee acknowledged that it would be more difficult to show a statistically significant treatment effect in people with less-severe disease at baseline. It recognised that only including people with more severe disease in the studies could affect the size of the estimated treatment effect. It was aware that an ongoing randomised controlled trial (CL301) comparing the safety and efficacy of burosumab with conventional therapy would provide more robust evidence. The committee recognised that the lack of randomised controlled trial data substantially reduced the robustness of the clinical-effectiveness comparison. To estimate the relative treatment benefit of burosumab compared with conventional therapy, the company presented a naive comparison of observed outcomes and a matched comparison (based on propensity score methods). The committee agreed that differences in baseline disease severity in CL201 and CL002 limited the usefulness of the naive comparison. It understood that the matched comparison of these studies went some way to addressing this, but acknowledged the ERG's concerns that there were limitations in a matched comparison with a limited number of covariates. The committee noted that the company did not provide comparative evidence for children aged 1 to 4 years, and agreed a robust assessment of clinical effectiveness in this group would be challenging. It concluded that the presented evidence was limited, and agreed that there would be uncertainty in its assessment of clinical effectiveness.

4.8 The committee noted that there were no data in young people aged 13 to 17 years, but that this age group is covered by burosumab's marketing authorisation. It recognised that evidence collection in this age group would be challenging. The committee noted that people in this age group might stop burosumab treatment during a clinical study because their bones would mature, but that the timing of this would vary between people. It accepted that this could interfere with the collection of clinical-effectiveness data in this age group. The committee considered whether there might be a biological reason why XLH in people aged over 12 years would have a different response to treatment. The clinical expert explained that puberty is an important time for bone growth, and one of the patient experts explained that sometimes the biggest deterioration in rickets and leg bowing occurs in people aged between 11 and 16 years. The committee considered that people may benefit more from burosumab treatment in this period, but emphasised that there was no evidence to support this. The company noted that it is developing a European registry and running disease monitoring programmes in the United States and Japan to generate more data in young people. The committee agreed that it would be beneficial to consider any data available in this age group. It concluded that the lack of evidence for the effects of burosumab in people aged between 13 and 17 years was a significant limitation.

Study outcomes

4.9 The committee noted that the key outcomes from the clinical trials, RSS and Radiographic Global Impression of Change (RGI-C), focused on the bone manifestations of XLH. It recognised that RSS and RGI-C would not capture changes in metabolic manifestations of XLH. The ERG explained that these measures do not capture all aspects of XLH symptoms and progression. The patient experts explained that bone defects (in particular bowing of arms and legs) are important aspects of XLH, but that other aspects of the condition also substantially affect their lives. A clinical expert advised that, with conventional therapy, there is a correlation

between changes in bone symptoms (assessed using X-rays) and other aspects of the condition. The committee concluded that RSS and RGI-C are informative outcome measures to quantify the clinical effectiveness of burosumab in children, and that other outcomes are also relevant to capture manifestations of XLH beyond rickets.

Clinical-effectiveness results

4.10 The committee discussed the clinical-effectiveness results presented for bone defects (RSS and RGI-C); in particular:

- Children aged 1 to 4 years (CL205): treatment with burosumab resulted in an improvement in RSS and RGI-C. Total RSS improved by 59% from baseline (2.92) to week 40 (1.19) with burosumab.
- Children aged 5 to 12 years (CL201 and CL002): there was a 58% improvement in total RSS score from baseline (1.92) to week 64 (0.81). These findings were supported by improvements in RGI-C.

4.11 The naive and matched comparisons of CL201 and CL002 consistently showed that burosumab improved bone defects (measured by RSS and RGI-C) more than conventional therapy. Further findings related to bone defects cannot be presented here because they have been deemed academic in confidence by the company. The committee also considered data on growth (change in standing height and velocity), mobility (6-minute walk test distance) and physical function and pain (Pediatric Orthopedic Society of North America-Pediatric Outcomes Data Collection Instrument [POSNA-PODCI]). Treatment with burosumab resulted in an improvement in all of these outcome measures compared with baseline values; the results are academic in confidence and cannot be reported here. The committee recognised that the clinical evidence suggested that treatment with burosumab was associated with improvements in bone defects, both compared with pre-treatment and compared with conventional therapy. It also agreed that burosumab was likely to improve symptoms of XLH beyond bone defects. The committee concluded that

the clinical evidence suggested that burosumab was more clinically effective than conventional therapy.

4.12 The committee considered the clinical significance of the findings from the studies. It recalled its concern about the limitations of the clinical evidence base (see section 4.7). However, it also recalled the comments from patient and clinical experts, which highlighted experiences suggesting that the improvements associated with burosumab had a substantial impact (see section 4.6). It acknowledged that data from CL301 would resolve some of this uncertainty when available. The committee concluded that the clinical evidence, although limited and uncertain, suggested that burosumab provided meaningful clinical benefits for people with XLH.

Long-term effectiveness

4.13 The committee discussed the long-term impact of improving skeletal deformities from a young age. The company highlighted that burosumab may reset people's bone architecture, and that correcting or preventing skeletal deformities before bone growth stops is expected to result in lifelong benefits. The committee recognised that the only opportunity to correct skeletal deformities was in childhood. The clinical experts reiterated that skeletal deformity is not the only manifestation of XLH, explaining that even if bone defects are corrected in childhood, people will continue to have symptoms and be at risk of new bone defects into adulthood. The company acknowledged that burosumab cannot directly affect XLH in the long term after treatment stops, but it noted that there will be lifelong benefits from correcting skeletal deformities in children. The committee acknowledged that this implied that burosumab would not affect the progression of bone manifestations of XLH during adulthood (for example, increased risk of osteomalacia and accompanying stress fractures and pain) or other ongoing aspects of the condition such as metabolic effects of low phosphate (for example, muscle weakness and fatigue; see section 4.1). The committee concluded there would be long-

term benefits from fixing or preventing childhood skeletal deformities, but agreed that burosumab would not affect other aspects of XLH in the long term.

Adverse effects

4.14 The committee considered the adverse effects of burosumab and conventional therapy. It acknowledged that the frequently occurring adverse events in the clinical trials were consistent with those expected in a trial setting. It noted that the only notable treatment-related adverse reactions were due to the subcutaneous administration of the treatment. The committee recalled comments from the patient and clinical experts stating that conventional therapy resulted in a variety of unpleasant side effects (see section 4.2). The committee concluded that the adverse effects associated with burosumab were more manageable than those with conventional therapy.

Cost to the NHS and value for money

Economic model

4.15 The company presented an economic analysis comparing burosumab with conventional therapy. This was based on a Markov model with 4 health states based on RSS: healed (RSS of 0), mild (RSS of 0.5 to 1.0), moderate (RSS of 1.5 to 2.0), and severe (RSS of 2.5 or more). The committee discussed in detail whether defining health states using a measure of bone defects (RSS) was a suitable proxy for disease severity and progression in people with XLH. It recalled that RSS is a measure relevant to children with growing skeletons (see section 4.9), and recognised that it would not capture new bone disease in adults or other manifestations of XLH. However, the clinical experts explained that RSS and other aspects of XLH are correlated. The committee considered that, in the absence of an alternative measure of disease severity in XLH, RSS was an acceptable and measurable proxy. It concluded that the model

structure adequately captured the disease progression of XLH in children, and agreed that the results from the economic model could be considered in its decision-making.

4.16 To model transitions between the health states of the economic model, the company used data from CL205 and CL201 and from a UK chart review study. Transition probabilities for people having burosumab were based on RSS data from CL205 (children aged 1 to 4 years) and CL201 (children aged 5 to 12 years and extrapolated to young people aged 13 years and over; licensed dose group only). The committee recalled that there was no clinical evidence for people aged between 13 and 17 years (see section 4.8). It agreed that extrapolating transition probabilities based on trial data for people aged 5 to 12 years to young people aged over 12 years introduced additional uncertainty. Data from the review of UK patient charts was used to generate transition probabilities in the conventional therapy arm. The ERG noted that the company's approach for estimating transition probabilities was theoretically flawed and corrected for this, although this had a negligible effect. The committee highlighted that the assumed transition probabilities implied that people having burosumab could not deteriorate (as measured by RSS). It considered that generating the transition probabilities from the trial data was appropriate, although it acknowledged that the very small population sizes in the trials introduced uncertainty into the model. The committee was also aware that the transition probabilities were based on trial data over 1 year, but were applied to all model cycles during childhood. It noted that there was no evidence for the effects of burosumab over 2 or more years that could inform later transition probabilities. The committee concluded that the transition probabilities were uncertain but acceptable for decision-making.

Model assumptions

4.17 The company assumed that when treatment was stopped (that is, when growth stopped) people would remain in their current health state for the rest of the modelled time horizon. The committee noted that, in the model, nearly all people having burosumab were in the healed health state by the time treatment was stopped, whereas there was a distribution of people across the different health states for conventional therapy. The committee queried the plausibility of this prediction. The committee recalled its conclusion that there would be long-term benefits from fixing or preventing skeletal deformities in childhood, but agreed that burosumab did not affect other aspects of XLH in the long term (see section 4.13). It also recalled that skeletal aspects of XLH are expected to progress during adulthood (see section 4.1), and considered that the fact that some people continue to have conventional therapy in adulthood (despite its side effects) implied that the disease had not stabilised. The committee was aware that there was no evidence on the long-term progression of XLH after burosumab treatment in childhood. It concluded that assuming lifetime disease stabilisation after stopping treatment was unrealistic, but that the nature of disease progression was unknown.

4.18 The committee considered how to incorporate long-term disease progression in the economic modelling. It noted the ERG's scenario analysis in which it assumed that, after 20 years, people in the burosumab arm would move down to the next (more severe) health state utility value (see section 4.20). The ERG explained that it adopted this approach because of limitations in the model and the lack of evidence to inform transition probabilities in adulthood, but acknowledged that this was simplistic. The company highlighted that it was inappropriate to only apply a utility decrement to the burosumab group when it was also assumed that those on conventional therapy had stabilised. The committee agreed that an assumption of disease progression should be applied to both burosumab and conventional therapy. It considered the ERG's approach,

and discussed whether waiting 20 years after treatment stopped was an appropriate time frame. A patient expert explained that some people could manage without treatment in their 20s and 30s but might resume treatment in their 40s as symptoms increased in severity. Conversely, it heard from the company that the metabolic effect of an injection of burosumab would not be identifiable after 1 week. The committee considered that the duration of disease stabilisation and persisting benefits of burosumab would vary between individuals and were uncertain. The committee also considered the size of the utility decrement as the treatment effect waned. It noted that the ERG's approach applied a utility decrement that was the same size as the decrement seen with normal aging over 40 years. The committee recognised that there was no evidence available to estimate the size of the most appropriate utility decrement, and it agreed that the magnitude of the decrement was uncertain. Overall, the committee considered that the ERG's approach was purely illustrative of the potential effect of the assumption of disease stabilisation. It noted that a more robust approach would have been to apply health state transitions later in life, but it recognised that there was insufficient evidence to do this. The committee acknowledged that the analysis incorporating the utility decline after 20 years was uncertain. It concluded that, in the absence of an alternative, it could consider the ERG's approach for decision-making, but would also take into account analyses without this decline.

4.19 The company base case incorporated a non-reference-case discount rate of 1.5% for costs and benefits because the benefits of treatment are expected to be substantial and sustained over a lifetime. The committee was aware that NICE's guide to the methods of technology appraisal (2013) and its interim process and methods of the highly specialised technologies programme (2017) states that a non-reference-case rate of 1.5% may be used when: treatment restores people to full or near-full health when they would otherwise die or have severely impaired lives; if it

is highly likely that there will be long-term benefits; and if the treatment does not commit the NHS to significant irrecoverable costs. The committee recalled its conclusions about long-term treatment benefit (see sections 4.13, 4.17 and 4.18). It acknowledged that there would be a lifetime effect from correcting skeletal deformities in children, and therefore that burosumab had the potential to resolve one of the most important aspects of XLH. However, the committee agreed that it was unlikely that burosumab would restore people to normal or near-normal health because symptoms of XLH are expected to continue and even progress in adulthood. In particular, it highlighted that the fact that some people choose to continue with conventional therapy into adulthood (despite serious side effects) illustrated that this was not consistent with 'normal or near-normal health'. Moreover, if there is established bone deformity at the time burosumab treatment starts, this damage may not be resolved. The committee also recalled the substantial uncertainties about the long-term benefits of burosumab and, in particular, the uncertainty associated with the lack of randomised controlled trial data. It concluded that, on balance, the criteria for deviating from the reference case discount rate of 3.5% for costs and benefits were not met.

Utility values

4.20 To model health-related quality of life, the company conducted a utility study in which vignettes describing the modelled health states were developed. The vignettes were valued using the EQ-5D-5L by 6 clinicians experienced in treating XLH. The committee noted that the utilities were scored by clinicians not patients, and were not taken directly from trials, which were limitations of the data. The vignettes assumed that all aspects of quality of life were worse in more severe health states (that is, there was perfect correlation between RSS and all aspects of quality of life). The ERG highlighted that the company made adjustments to the utility values in the published report of the study because not all experts provided estimates for all health states. It noted that these adjustments

reduced the utility values in the severe health state and increased the values in the healed state; because all people having burosumab were predicted to be in the healed health state for most of the model time horizon (that is, after disease stabilised; see section 4.17), the adjustment favoured burosumab. The committee considered that the important differences between the adjusted and unadjusted utilities illustrated the serious limitations of the available utility data. It was not convinced that it was necessary to adjust the utility values, but had very little evidence on which to choose whether to use the adjusted or unadjusted utility values. On balance, the committee concluded that it would be more appropriate to consider analyses based on the unadjusted utility values in its decision-making.

Probabilistic analysis

4.21 The committee discussed the probabilistic analyses presented by the company and ERG, and was aware that the results differed substantially from each other and from the deterministic analysis. The company and the ERG explained that they explored the use of prior distributions in a Bayesian approach to generating transition probabilities in the probabilistic analysis. They did this to try and capture the uncertainty in the transition probabilities, and to resolve issues that resulted from having limited data, particularly about transitions that might be expected to occur occasionally but were not seen in the studies. The committee understood that both the company and the ERG used a uniform prior distribution, but the company used a factor of 0.05 whereas the ERG provided results from a range of values with a preference for using a factor of 1. The committee noted that the company's approach increased the incremental cost-effectiveness ratios (ICERs) compared with the deterministic analysis, and that the ERG's preferred factor caused a substantially greater increase in the ICER. The committee considered that the ERG's preferred factor placed too much emphasis on the prior distribution, and led to results that lacked face validity. In particular, the committee

highlighted that incorporating uncertainty in the transition probabilities through the probabilistic analysis was expected to increase the uncertainty around the cost effectiveness but not to dramatically increase the result (as was seen). The committee considered that the substantial differences between the probabilistic and deterministic ICERs, and between probabilistic scenarios, were driven by the choice of prior distribution, and not by other issues with the probabilistic analyses. It concluded that the probabilistic analyses outlined the magnitude of the uncertainty in the results, and that the lack of observed data affected the robustness of the economic analyses, but that the mean ICERs from the probabilistic analyses were not suitable for decision-making.

Additional assumptions and uncertainties

4.22 The committee acknowledged that there were several other assumptions and uncertainties in the economic model. The ERG noted that the company based the starting distribution of health states and weight on the CL205 and CL201 studies and UK growth charts. It suggested that this was unnecessary as data were available from the UK chart review. The ERG noted that treatment-related adverse events were not included in cost or utility calculations in the model. It expected the inclusion of these costs and utility decrements to have a modest effect on the economic results. The committee recognised that there were additional uncertainties in the economic model, but concluded that the presented model was adequate for decision-making.

Cost-effectiveness analysis results

4.23 The committee considered the results of the economic analysis, taking into account the company base case and the ERG's exploratory analyses. The ICERs have been deemed commercial in confidence by the company, so cannot be reported. The committee noted that the incremental quality-adjusted life year (QALY) gain associated with burosumab estimated in the company's base case was 10.30, compared

with 3.95 in the ERG preferred analysis. The committee considered that the most plausible scenario was that based on the following amendments to the company base case:

- incorporating a cost for adverse events (see section 4.22)
- correcting burosumab transition matrices to account for a flaw in the methodology (see section 4.16)
- using unadjusted utility values from the utility study (see section 4.20)
- discount rate of 3.5% for costs and benefits (see section 4.19).

The committee also took into account the analysis that included a decline in utility after 20 years (to account for disease progression; see section 4.18). Based on this analysis, the committee noted that the most plausible incremental QALY gain associated with burosumab ranged from 3.95 QALYs (with the utility decline) to 4.91 QALYs (without the utility decline). The committee was aware of uncertainty in the presented analyses, but concluded that these scenarios were sufficient for decision-making.

4.24 The committee understood that the interim process and methods of the highly specialised technologies programme (2017) specifies that a most plausible ICER of below £100,000 per QALY gained for a highly specialised technology is normally considered an effective use of NHS resources. For a most plausible ICER above £100,000 per QALY gained, judgements about the acceptability of the highly specialised technology as an effective use of NHS resources must take account of the magnitude of the incremental therapeutic improvement, as revealed through the number of additional QALYs gained. The undiscounted incremental QALYs in the in the committee's preferred analysis were between 8.29 and 13.56. The committee concluded that burosumab could meet the criteria for applying a QALY weight, and that, under its most plausible assumptions, a QALY weighting of between 1 and 1.36 can be applied.

4.25 The committee noted that the range of ICERs based on its most plausible analysis was substantially higher than the level that can be considered an effective use of NHS resources for highly specialised technologies, even when QALY weighting was applied.

Impact of the technology beyond direct health benefits and on the delivery of the specialised service

4.26 The committee understood that XLH had a significant impact on children, parents and often several generations of a single family. The patient experts explained that this limited the care that could be provided within the family. The committee understood that XLH can also have a significant impact on children's attendance at school, with effects on their education. The patient experts also explained that XLH has affected their working choices, and subsequently their finances. The committee understood that symptoms in adults could reduce productivity or attendance at work. It accepted that burosumab may reduce some of these effects. The clinical experts explained that the dosing regimen of burosumab was more practical than conventional therapy, and would be less disruptive to the lives of children. The committee recognised that burosumab had an impact beyond health benefits, but it noted that the full impact of these benefits had not been quantified. The committee considered these benefits in its decision-making.

4.27 There is not a specified service for XLH and rare bone diseases in the NHS, but the NHS commissioning expert explained that there would be greater standardisation of the treatment pathway if access to burosumab was restricted to expert centres. The company highlighted its discussions with NHS England, noting that burosumab would only be prescribed by small number of specialist centres that are members of the European Reference Network on Rare Bone Disorders. The committee noted the company's intention to offer maintenance doses of burosumab via a homecare provider – initially administered by a nurse, and potentially

followed by administration by the patient or a carer. The clinical experts noted that investment may eventually be needed to train parents or carers in giving subcutaneous injections. The committee noted that regular travel to specialist centres could have an impact on education and family life, until homecare delivery is possible. It acknowledged that burosumab may have an additional effect on the delivery of highly specialised services.

Managed access agreement

4.28 The committee noted that there were uncertainties in the evidence base, which suggested that collecting additional evidence may be of value. It therefore noted that a managed access arrangement (MAA) might be a possible route to address and resolve some of the uncertainties. However, the committee considered that an MAA would only be appropriate if it could be shown that burosumab had a plausible potential to be considered an effective use of NHS resources within the context of highly specialised technologies. It emphasised that, if an MAA were to be considered, the evidence collection should focus on the key uncertainties and, in particular, health benefits over time. The committee recognised that some key uncertainties could potentially be resolved through an MAA; for example: the effects of burosumab over 2 or more years; the effects on people aged over 12 years; the effects of burosumab across a wider range of disease severity; and the utility scores in the economic model. However, it considered that the duration of treatment benefit was one of the most important uncertainties (see sections 4.13, 4.17 and 4.18), but recognised that an MAA would be unlikely to resolve this. The committee noted that the clinical evidence comparing burosumab with conventional therapy was limited, and the availability of data from the randomised control trial (CL301) would improve the clinical evidence base. The committee concluded that although an MAA could help resolve some of the uncertainties in this evaluation, it could not address the key uncertainty relating to long-term treatment benefit. As a result, and taking into account the fact that burosumab did not have the plausible potential

to be considered a good use of NHS resources, the committee concluded that it was unlikely that a managed access agreement would be appropriate for burosumab.

Other factors

4.29 The committee recognised that burosumab is a treatment for children with growing skeletons, and discussed whether any additional considerations were needed to take account of the nature of the population. It recognised that treating XLH in children offers the only chance of normal skeleton development, and that this has a lasting impact over the person's lifetime. However, the committee considered that the long-term benefits of correcting skeletal deformities in children had been accounted for in the economic model. It highlighted that it was aware that the population included children and took this into account in its decision-making. The committee concluded that no additional considerations were needed.

4.30 No other equalities issues were highlighted.

4.31 The committee discussed whether they believed that burosumab was an innovative treatment for people with XLH. It recognised that burosumab was the first treatment that inhibits the action of excess FGF23, so impacting on the pathophysiology of XLH. It also acknowledged comments from patient and clinical experts that the administration of burosumab is less burdensome than current treatment options. It agreed that this was a benefit of the treatment but did not represent an innovation. The committee concluded that burosumab was innovative in its mechanism of action, but not in its administration.

4.32 The clinical and patient experts explained that burosumab was expected to be associated with a reduced need for surgical intervention. The committee was concerned that the health benefits from avoiding surgery had not been fully captured within the vignette study. It considered any reduction in the need for surgical intervention could represent a significant

benefit to people with XLH. It agreed that fully including these benefits in the model would favour burosumab and subsequently reduce the ICER. However, the committee concluded that it did not expect that including benefits from avoiding surgical procedures would change its decision.

Conclusion

4.33 The committee acknowledged that XLH is a rare condition that can have a substantial impact on patients and families. It was aware that skeletal deformities arise in childhood and progress into adulthood, causing lifelong disability and pain. It was also aware that bone defects in childhood are not the only manifestation of XLH, and that metabolic manifestations of XLH (such as fatigue and muscle weakness) often have significant impacts on children and adults. The committee noted the clinical-effectiveness evidence, and considered that a robust comparison of burosumab with conventional therapy could not be made based on the evidence presented. However, it acknowledged that data from the randomised control trial (CL301) would help resolve this. Overall, the committee considered that the available evidence was suggestive that burosumab would provide meaningful clinical benefits. Taking into account the most plausible assumptions in the economic model, the committee acknowledged that burosumab could meet the criteria for QALY weighting. However, it nevertheless considered that the ICERs were above the range that can be considered an effective use of NHS resources for highly specialised technologies, and emphasised that they were also uncertain. Therefore, the committee did not recommend burosumab as an option for treating XLH.

5 Proposed date for review of guidance

5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. This guidance should be reviewed in full if burosumab is

considered for use in adults (for example, if the marketing authorisation is expanded). NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Jackson

Chair, highly specialised technologies evaluation committee

June 2018

6 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

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

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.

NICE project team

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

Thomas Paling
Technical Lead

Ian Watson
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Joanne Ekeledo
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