NICE National Institute for Health and Care Excellence

NICE guidance

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

Highly specialised technologies 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, 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 bones. It is recommended only if the company provides burosumab according to the commercial arrangement.

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, disagreeable taste and unpleasant side effects.

Clinical trial evidence suggests that burosumab provides short-term clinical benefits in children aged between 1 and 12 years. It is expected that there is some lifetime benefit for people having burosumab because it can prevent irreversible bone damage, which could lead to less pain and a better quality of life as people get older. There are uncertainties in the clinical evidence (including a lack of evidence in young people aged between 13 and 17 years, and on the long-term consequences of progressive bone disease and ongoing metabolic symptoms of XLH, which would not be affected by burosumab). However, burosumab is likely to provide important clinical benefits for people with XLH.

Taking into account the most plausible assumptions in the economic model, burosumab is considered to provide value for money within the context of a highly specialised service. Burosumab is therefore 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 and can be the source of continuing pain. Other manifestations of XLH include dental problems and hearing loss. Adults with XLH can have symptoms such as osteomalacia (softening of the bones, which causes an increased risk of stress 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 fibroblast growth factor 23 (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. For this appraisal, burosumab had 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'. In October 2022, this was updated to a full marketing authorisation, in which burosumab is licensed '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'.

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 bones stop 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). 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. It is the company's responsibility to let relevant NHS organisations know details of the discount.

4 Consideration of the evidence

The evaluation committee (see section 7) 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 effect on the child and their family. The clinical experts explained that many manifestations of XLH mean children with the condition are vulnerable to bullying, which further exacerbates its emotional and psychological effects. The committee recognised that bone defects will become permanent if the condition is untreated while bones are growing. This can result in skeletal abnormalities continuing into adulthood, and lifelong disability and pain. The patient experts noted from their experiences of XLH that painful symptoms result from established bone deformities and associated surgeries. 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 acknowledged comments received during consultation that dental abscesses cause significant detrimental effects on the quality of life of adults and children. The committee agreed that, in the absence of evidence, it was difficult 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, contribute to poor adherence to this therapy (see section 4.16), and the committee recognised that this was an issue. The patient experts explained that, even when children have treatment 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 heard from the patient experts that surgery is distressing and can be disruptive to education or work. One of the patient experts also explained that they have had continued bone and joint pain after having corrective surgery (see section 4.1). 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 is 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 who would benefit more from treatment or who 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 clinical experts suggested that there may be some benefit to continuing treatment into adulthood, and noted that about half of people who stop conventional therapy will start again when symptoms return. They noted that it is not uncommon for people who stop treatment to have stress fractures over the following 9 to 12 months, which causes significant pain. The committee acknowledged comments received during consultation stating that prolonged use of conventional therapy can cause serious side effects (kidney stones and hypercalcaemia). It concluded that XLH is a heterogeneous condition, and agreed that the benefit of continuing conventional therapy into adulthood would vary between individuals.

4.6 The committee acknowledged that, if the symptoms of XLH were to return after stopping burosumab, there may be consideration of whether continued treatment would be beneficial. It acknowledged that continued treatment with burosumab into adulthood might seem desirable, but noted that conventional therapy would have to be considered because 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 only be considered for use in children and young people.

Impact of the new technology

Patient and clinician perspectives

4.7 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. They highlighted that only a small proportion of people – perhaps those with more mild disease and good adherence to treatment – 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

4.8 The main clinical evidence submitted by the company came from 4 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)
- CL301: an ongoing multicentre open-label randomised controlled trial including 61 children aged 1 to 12 years, comparing the efficacy and safety of burosumab with conventional therapy
- 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 were important differences between the studies, which made a comparison of results difficult to interpret. It noted that CL301 only included people with severe bone defects (that is, a Rickets Severity Score [RSS] of 2 or more), and that there were different dosing regimens for burosumab across studies. The committee understood that these differences could be associated with differences in treatment effect, and agreed that it should be taken into account when interpreting the clinical-effectiveness results.

4.9 The committee discussed the generalisability of CL301 to the XLH population in England, and noted that a population with an RSS of 2 or more may not be representative of the XLH population treated in clinical practice. 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 have affected the size of the estimated treatment effect. The committee noted that, before initial results from CL301 were available, there was no comparative evidence for children aged 1 to 4 years, and that the comparison of children aged 5 to 12 years was done by naive and matched comparisons of CL201 and CL002, which were highly uncertain. The committee acknowledged that CL301 provided comparative data from a randomised controlled trial for children aged 1 to 12 years, so went some way to addressing the uncertainties in the clinical evidence. However, it agreed that, because of restrictive inclusion criteria and small patient numbers, there was still uncertainty about the magnitude of the treatment effect. It concluded that CL301 provided a more robust comparison of burosumab with conventional therapy than was previously available, but that the magnitude of the relative treatment benefit was still uncertain.

4.10 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 experts 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

4.11 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. The company noted that outcomes relating to walking ability, pain, functional mobility, growth, fatigue and quality of life were all captured in CL301. The committee recalled that dental abscesses substantially affect quality of life in children and adults with XLH (see section 4.1). It agreed that it would have liked to have considered the effect of treatment on dental problems. The company noted that dental problems had not been captured as a study endpoint in the studies presented, but noted that it had plans to collect data on dental problems in a proposed long-term real-world-data programme. A clinical expert advised that there is a correlation between changes in bone symptoms (assessed using X-rays) and other aspects of the condition. The committee acknowledged this, and noted that some of the wider effects of XLH would also be captured in measures of quality of life. It 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

4.12 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) in patients who had burosumab. These findings were supported by improvements in RGI-C.
- Children aged 1 to 12 years (CL301): at week 40 there was a greater improvement in RGI-C global scores in patients who had burosumab (1.92) compared with those who had conventional therapy (0.77). These findings were supported by improvements in RSS.

4.13 The committee noted that results from 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. It considered that the results from CL301 were broadly consistent with those seen in the comparisons of CL201 and CL002. It agreed that the findings from CL301 were reassuring, and recognised that the clinical evidence suggested that treatment with burosumab was associated with improvements in bone defects. Further findings related to bone defects cannot be presented here because they have been marked 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), fatigue, physical function, mobility and pain. It noted that there was a trend towards improvement in all of these outcome measures, and that improvements were larger for people who had burosumab compared with conventional therapy; the results are academic in confidence and cannot be reported here. The committee recalled that there is a correlation

between changes in bone symptoms and other aspects of the condition (see section 4.11). It accepted that, while people are on treatment, burosumab is 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.

4.14 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 4.8). It also recalled the comments from patient and clinical experts, which highlighted experiences suggesting that the improvements associated with burosumab had a substantial effect (see section 4.7). It acknowledged that data from CL301 had resolved some of the uncertainty in the clinical evidence base, although some uncertainties remained. While acknowledging these, the committee concluded that the clinical evidence suggested that burosumab provided meaningful clinical benefits for people with XLH.

Long-term effectiveness

4.15 The committee discussed the long-term effects 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, and that doing so could provide important long-term benefits. The clinical experts reiterated that skeletal deformity is not the only manifestation of XLH, explaining that people will continue to have symptoms and be at risk of new bone defects into adulthood even if bone defects are corrected in childhood. The company acknowledged that burosumab cannot directly affect XLH in the long term after treatment stops, but 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 company stated that painful symptoms in adults with XLH are mostly caused by bone deformity, not

osteomalacia. The committee recalled comments from one of the patient experts that pain was a result of established deformity and surgery (see section 4.1). Conversely, it recalled that many patients who stop having conventional management have painful symptoms, including stress fractures, soon after (see section 4.5), and noted that a similar effect might be seen after stopping burosumab (when bone growth stops). The committee acknowledged that the manifestations and severity of XLH would vary in adults, and agreed that the cause of painful symptoms could not be isolated. It concluded that there would be important long-term benefits from fixing or preventing childhood skeletal deformities, although burosumab would not affect other aspects of XLH in the long term.

Adverse effects

4.16 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 for burosumab were due to the subcutaneous administration of the treatment. The committee recalled comments from the patient and clinical experts stating that conventional therapy results 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

4.17 The company presented an economic analysis comparing burosumab with conventional therapy. This was based on a Markov model with 4 health states using 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 bones (see section 4.11), 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 in children. The committee considered that, in the absence of an alternative measure of disease severity in XLH, RSS was an acceptable and measurable proxy. In response to the evaluation consultation document, the company presented a revised analysis using an amended version of the economic model. This incorporated a commercial arrangement and changes to transition probabilities, costs and utility values. The committee concluded that the model structure adequately captured the disease progression of XLH in children, and agreed that the revised analysis results from the economic model could be considered in its decision-making.

4.18 To model transitions between the health states of the economic model, the company used data from CL205, CL201, CL301 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), CL201 (children aged 5 to 12 years; licensed dose group only) and CL301 (children aged 1 to 12 years). The company explained that the inclusion criterion in CL301 of an RSS of 2 or more meant that data from CL205 and CL201 were needed to model transitions in less severe health states. The ERG highlighted that differences in the study populations reduced the suitability of pooling results from the different studies. It also noted that, in its revised analysis, the company calculated a single transition probability matrix for all ages, so assumed that treatment effect does not depend on age. The committee acknowledged the ERG concerns, but agreed that it did not expect this change to have a substantial effect on the analysis. It recognised that the inclusion of data from CL301 allowed for more information to be used in calculating the transition probabilities and agreed this was appropriate. The committee recalled that there was no clinical evidence for people aged between 13 and 17 years (see section 4.10). 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 CL301 and the review of UK patient charts were used to generate transition probabilities in the conventional therapy arm. 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 about 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

4.19 In its revised analysis, the company estimated the age at which growth stops to be 14 years in girls and 16 years in boys. This was based on the mean age of final height defined as a growth velocity of less than 2 cm per year. The committee noted that, in the company's original base case, the treatment stopping age was 16 years in girls and 17 years in boys. It acknowledged that stopping treatment earlier had a substantial effect on the estimated treatment costs and hence the incremental cost-effectiveness ratios (ICER). It was aware that the earlier treatment stopped in the model, the lower the ICER, so the original base case was more conservative than the revised base case. The ERG stated that the company had misinterpreted the growth charts and that, based on the proposed definition of final height, the treatment stopping ages should be 15 years in girls and 17 years in boys. The committee considered how final height would be determined in clinical practice. One clinical expert explained that they used radiographs of the hands to identify closure of the growth plate. The committee understood that bone growth stops after the growth plate has closed. It recognised that there was value in using an objective measure, and recommended that an objective measure of growth completion should be used in clinical practice. Alternative clinical advice was that growth completion as identified by a hand radiograph would be expected to happen at about the same time as when it is identified by final height defined as a growth velocity of less than 2 cm per year; the expert considered that radiographs are not necessary. The committee was reassured that, regardless of which approach were to be adopted in practice, the model would be suitable for decision-making because treatment would be unlikely to continue for longer than estimated in the company's economic modelling. The committee concluded that treatment stopping age was an important variable in the assessment of cost effectiveness,

and agreed that it would consider the effect of the different stopping ages on the results.

4.20 The company assumed that, when treatment was stopped (see section 4.19), 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. It queried the plausibility of this prediction, recalling its conclusion that there would be long-term benefits from fixing or preventing skeletal deformities in childhood. However, it agreed that burosumab would not affect other aspects of XLH in the long term (see section 4.15). The committee 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 condition 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.

4.21 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 4.24). 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 there was no evidence to support a greater long-term utility decline for people who had burosumab in childhood than for those who had conventional management. It stated that, if applied, a utility decrement should be applied to both groups. The committee accepted that the ERG's approach was intended to capture a waning of burosumab treatment effect, but that the company had not intended to imply a direct effect of treatment after it stopped (that is, the long-term benefit of burosumab was solely through improving the patient's health state at the start of adulthood). It acknowledged that, if there was a long-term direct treatment effect, the ERG's approach might be reasonable, but that there was no evidence

to support this. Conversely, the committee considered that, if the decline in utility captured the long-term progression of disease, an assumption of disease progression should be applied to both burosumab and conventional therapy. It considered the ERG's approach, and agreed that the duration of disease stabilisation and persisting benefits of burosumab would vary between individuals and were uncertain. It also noted that the ERG's approach applied a utility decrement that was the same size as the decrement seen with normal ageing 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 uncertain and was purely illustrative of the potential effect of reducing the long-term treatment benefit of burosumab, and therefore did not inform the most plausible scenario for decision-making.

4.22 In its response to the evaluation consultation document, the company implemented a new approach to model long-term disease progression. It asked a group of experts to value (using EQ-5D-5L) the quality of life of people with XLH aged 18 years, 40 years and 60 years, based on health state vignettes. Using these estimates, the company estimated a decrease in quality of life over time across the model health states. The ERG emphasised that this did not capture any waning in the long-term treatment effect of burosumab. The committee acknowledged that the company's approach incorporated more information than the ERG's illustrative method, and appeared to capture long-term disease progression, but recognised there were limitations with both methods. It concluded that, in the absence of long-term evidence, the company's approach was more appropriate for decision-making purposes, but acknowledged that the estimation of long-term outcomes remained highly uncertain.

Discount rate

4.23 The company's 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; when this is sustained over a very long period (normally at least 30 years); 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 4.15, 4.19 and 4.21). 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. The committee agreed that burosumab might restore people's skeletons to normal or near-normal. However, it considered that it was unlikely that the drug would restore people's overall health to normal or near-normal because symptoms of XLH are expected to continue and even progress in adulthood. In particular, the committee highlighted that the fact that some people choose to continue with conventional therapy into adulthood (despite unpleasant, and potentially serious, side effects) illustrated that this was not consistent with 'normal or near-normal health'. Moreover, it noted that, 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. It concluded that the criteria for deviating from the reference case discount rate of 3.5% for costs and benefits were not met.

Utility values

4.24 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 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 explained that asking experts to value the quality of life of hypothetical people is not ideal, and generates results that are substantially uncertain. The company noted that some responses were not provided, and explained that it had inferred 1 value for the healed health state. The committee accepted that this inference was logical, and agreed that the

minor amendment to the utility values was appropriate. It concluded that the utility values were uncertain but, in the absence of an alternative, were acceptable for decision-making.

4.25 The committee considered the effect of XLH on caregivers. It recalled that, because of the genetic nature of XLH (see sections 2.1 and 2.2), many adults with the condition will often be carers for other affected family members. It recognised that this might make the effect on carers particularly acute. In its response to the evaluation consultation document, the company estimated the effect of XLH on caregivers of children with XLH using a 'disutility' value taken from a published study of people with limited mobility. The company highlighted that it was practically challenging to accurately model the full effect of XLH on caregivers. The ERG noted that the company's approach of using a published disutility value was broadly reasonable in this context. The committee questioned the appropriateness of the disutility value that was identified, although it welcomed the company's attempt to quantitatively estimate the effect on caregivers. The committee concluded that it was important to consider carer burden in its assessment of burosumab. It further concluded that it would take into account results including a quantitative estimate of carer burden, but because the estimate provided was not robust, it would also consider the burden qualitatively (using analyses in which the quantitative burden was omitted).

Probabilistic analysis

4.26 The committee discussed the probabilistic analyses presented by the company and the 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. However, 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 1.00. The committee noted that the company's approach increased the ICERs compared with the

deterministic analysis, and that the ERG's preferred factor caused a substantially greater increase in the ICERs. The committee considered that, with few observed data points, the ERG's preferred factor placed too much emphasis on the prior distribution, and led to model results (ICERs) 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 ICER (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, that the lack of observed data affected the robustness of the economic analyses, and that the mean ICERs from the probabilistic analyses were not suitable for decision-making.

Additional assumptions and uncertainties

4.27 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 because data were available from the UK chart review. In response to the evaluation consultation document, the company corrected a methodological error in the burosumab transition probabilities and incorporated adverse events costs in the model. 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

4.28 The committee considered the results of the economic analysis, taking into account the company base case, the ERG's exploratory analyses and the committee's preferred scenario. The committee considered that its preferred scenario was that based on the following amendments to the company's original

base case:

- incorporating a cost for adverse events (see section 4.27)
- correcting burosumab transition matrices to account for a flaw in the methodology (see section 4.17)
- incorporating data from CL301 into the transition probabilities for burosumab and conventional therapy (see section 4.18)
- using utility values from the vignette study with an additional inferred value for the healed health state (see section 4.24)
- incorporating the company's estimate of progressive utility decline (see section 4.22)
- discount rate of 3.5% for costs and benefits (see section 4.23).

The committee also took into account the age at which treatment is stopped (see section 4.19) and the effect of carer burden (see section 4.25). Based on the committee's preferred assumptions, and using the most conservative treatment stopping ages (16 years in girls and 17 years in boys) but omitting the caregiver disutility, the ICER was £149,565 per quality-adjusted life year (QALY) gained. Based on these assumptions and using the more optimistic treatment stopping ages (14 years in girls and 16 years in boys), and including the caregiver disutility, the ICER was £112,517 per QALY gained. In these scenarios, the incremental QALY gains associated with burosumab ranged from 5.52 to 15.99. The committee concluded that the ICER was in the range of £113,000 to £150,000 per QALY gained.

4.29 The committee understood that NICE's 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. Taking into account the incremental QALY gains (between 5.52 and 15.99), the committee concluded that

burosumab could meet the criteria for applying a QALY weight.

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

4.30 The committee understood that XLH has a significant effect on children, parents and often several generations of a single family. The patient experts explained that this limits the care that can be provided within the family. The committee understood that XLH can also have a significant effect on children's attendance at school, with effects on their education. The committee recalled a comment from the clinical experts that XLH made children vulnerable to bullying and teasing. It also acknowledged that XLH can affect relationships in adulthood. 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 effect beyond health benefits, but it noted that the full effect of these benefits had not been quantified. The committee considered these benefits in its decision-making.

4.31 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 a 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 patients and carers in giving subcutaneous injections. The committee noted that regular travel to specialist centres could have an effect 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 arrangement

4.32 The committee noted that there were many uncertainties in the evidence base, which suggested that collecting additional evidence may be of value. It considered that a managed access arrangement (MAA) might be a possible route to address and resolve some of the uncertainties. 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 long-term benefit of treatment was one of the most important uncertainties (see sections 4.15, 4.20 and 4.21), and recognised that an MAA would be unlikely to resolve this. The committee recalled a comment from the clinical experts that noted a correlation between changes in bone symptoms (assessed using X-rays) and other aspects of the condition (see section 4.11). It agreed that, if this relationship could be explored and quantified in a robust way, it could help to relieve uncertainty in the analysis of long-term outcomes and utilities. The committee considered that this research did not need to be done strictly within an MAA, but would nevertheless be valuable. It recognised 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. The committee concluded that, in this instance, an MAA would not be appropriate, but that further research would be highly valuable.

Other factors

4.33 The committee recognised that burosumab is a treatment for children with growing bones, 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 effect 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. No other equalities issues were highlighted.

4.34 The committee discussed whether it 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 fibroblast growth factor 23 (FGF23), so affecting 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.

4.35 The clinical and patient experts explained that burosumab was expected to be associated with a reduced need for surgical intervention. The committee recalled that surgical intervention was distressing and disruptive to children and parents (see section 4.2), and heard that repeated surgeries would be costly to the NHS. The committee was concerned that the health benefits from avoiding surgery had not been fully captured within the vignette study, and that the cost impact had also not been fully captured in the model. 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. The committee agreed that long-term monitoring of surgical intervention would allow a quantitative assessment of these benefits.

Conclusion

4.36 The committee acknowledged that XLH is a rare condition that can have a substantial effect 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 effects on children and adults. The committee noted that, although initial comparative evidence from early clinical trials was highly uncertain, the inclusion of data from CL301 reduced some of the clinical uncertainty. However, the committee noted that there were still no data available for people aged 13 years and over, which it agreed was a limitation. Overall, the committee considered that the available evidence was suggestive that burosumab would provide meaningful clinical benefits. While acknowledging the uncertainties, the committee considered that, when accounting for the incremental QALY gains and taking into account other benefits of burosumab that were not captured in the analysis (including the reduced need for surgery and effects beyond direct health benefits), burosumab is a cost-effective use of NHS resources for highly specialised technologies. Therefore, the committee recommended burosumab as an option for treating XLH in children and young people.

5 Implementation

5.1 Section 8(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, 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.

5.2 The Welsh Ministers have issued directions to the NHS in Wales on implementing NICE highly specialised technologies guidance. When a NICE highly specialised technologies 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 evaluation determination.

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

6 Recommendations for further research

6.1 A number of ongoing or proposed research studies have been noted in the evaluation of burosumab. Burosumab has a conditional marketing authorisation for the treatment of X-linked hypophosphataemia (XLH). The marketing authorisation is conditional on further data collection in 3 of the clinical studies considered in this evaluation: CL205; CL201; and CL301. Further to 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 aged 13 years and over. It also explained that there was a planned long-term real-world-data collection programme for burosumab.

6.2 In its evaluation of burosumab, the committee noted substantial uncertainty in several areas, and agreed that further research into the treatment benefit of burosumab in young people aged 13 years and over would relieve some of the clinical uncertainty in an age group covered by the marketing authorisation. The committee also noted that the additional evidence exploring the relationship between radiological measures of bone defects (that is, the Rickets Severity Score and the Radiographic Global Impression of Change) and health-related quality of life would help to address several key uncertainties in the economic analysis. Evidence on the progression of XLH over time and the long-term benefits of burosumab would also be valuable.

7 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
Technical Adviser

Joanne Ekeledo
Project Manager

Update information

April 2025: In September 2024, recommendation 1.1 was amended. This change was made in error and has been corrected back to the original wording.

September 2024: Recommendation 1.1 has been amended to match the updated marketing authorisation for burosumab, which has also been updated in section 3.1.

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