Cost-effectiveness of burosumab (Crysvita®) for the treatment of X-linked hypophosphataemia with radiographic evidence of bone disease in children one year of age and older and adolescents with growing skeletons.

The NCPE has issued a recommendation regarding the cost-effectiveness of burosumab (Crysvita®). Following assessment of the Applicant's submission, the NCPE recommends that burosumab (Crysvita®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the Applicant's (Kyowa Kirin Pharmaceuticals) economic dossier on the cost effectiveness of burosumab (Crysvita®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

National Centre for Pharmacoeconomics **March 2020**

Summary

In August 2019, Kyowa Kirin Pharmaceuticals submitted a pharmacoeconomic evaluation to support the reimbursement application for burosumab for the treatment of X-linked hypophosphataemia (XLH) with radiographic evidence of bone disease in children one year of age and older and adolescents with growing skeletons.

Burosumab is a recombinant human IgG1 monoclonal antibody that binds to and inhibits the activity of FGF23. By inhibiting FGF23, burosumab increases tubular reabsorption of phosphate from the kidney. It also increases the di-hydroxylation of vitamin D, increasing intestinal absorption of calcium and phosphate. Burosumab improves phosphate homeostasis and its major pathologic consequences (rickets and osteomalacia), and consequently aims to resolve the skeletal and non-skeletal manifestations of XLH. The EMA granted burosumab conditional marketing authorisation on 23 February 2018.

The recommended starting dose of burosumab is 0.8mg/kg, given every two weeks by subcutaneous injection. The dose should be titrated upwards to maintenance dose in 0.4mg/kg increments at four week intervals. The maximum dose is 2.0mg/kg (up to a maximum of 90mg).

The main comparator for this analysis was conventional therapy. Conventional therapy was defined as the use of oral phosphate (Phosphate Sandoz) and activated vitamin D (alfacalcidol).

1. Comparative effectiveness of burosumab

The Applicant included a number of studies across different populations. These included;

- Study CL301 (an on-going Phase 3 randomised controlled trial (RCT) (n=61) to study the efficacy and safety of burosumab vs conventional therapy (oral phosphate/activated vitamin D) in children aged one to 12 years old. The initial dose of burosumab was 0.8mg/kg subcutaneously every 2 weeks, increased to 1.2mg/kg

every 2 weeks if two consecutive pre-dose, fasting, serum phosphorus concentrations were below 1.03 mmol/L and serum phosphorus had increased by less than 0.16 mmol/L from baseline on a single measurement.

- Study CL201 was a Phase 2 open-label RCT comparing different doses of burosumab (burosumab in doses 0.1 to 2.0 mg/kg every 2 to 4 weeks) in children aged five to 12 years old (n=52):.
- Study CL205 was a Phase 2 open-label study to assess the safety, pharmacodynamics and efficacy of burosumab (burosumab at a target dose of 0.8 mg/kg every 2 weeks) in children aged one to four years old (n=13).
- Study CL002 was a retrospective longitudinal study of skeletal outcomes in children with XLH in children aged five to 14 years old (n=52):. Study inclusion required the use of conventional therapy (oral phosphate/activated vitamin D). Burosumab was not administered in this study.
- UK Chart Review (UK historical control study): a retrospective analysis of medical records of 43 patients, aged up to 18 years with XLH.

The primary outcome in Study CL301 was the change in rickets severity at week 40, assessed by the Radiographic Global Impression of Change (RGI-C) Scale; a 7-point ordinal scale with scores ranging from -3 (severe worsening) to +3 (complete healing). This was based on skeletal abnormalities on wrist and knee radiographs assessed by three independent paediatric radiologists. Patients in the burosumab group had significantly greater improvement in rickets as assessed by the RGI-C Scale at week 40 and week 64 (secondary outcome) compared with those in the conventional therapy group. Other secondary outcomes included phosphate levels, which were increased to the lower limit of normal in the burosumab group whereas there were minimal changes in the conventional therapy group.

The primary outcome in Study CL201, change in Rickets Severity Score (RSS) Total Score (least square mean) from baseline to week 40, was -1.1 and -0.7 at week 40 in the groups who had received burosumab every 2 weeks and every 4 weeks respectively ($p<0.001$ for both comparisons). A reduced RSS score indicates improvement in rickets severity. The RGI-C Scale score (least square mean) at week 40 was 1.66 and 1.47 in both groups. These

results indicated improvements in rickets in both groups at week 40 and this was maintained at week 64. Improved functional ability and decreased pain, as assessed by the Paediatric Orthopaedic Society of North America – Paediatric Outcomes Data Collection Instrument (POSNA-PODCI) questionnaire, was shown in the overall population at 64 weeks.

In Study CL205 the co-primary outcomes were safety and change from baseline to week 40 in fasting serum phosphorus concentration. The mean fasting serum phosphorous concentration increased from 0.81mmol/L to 1.12mmol/L. The least squares mean increase from baseline of 0.31mmol/L was significant, $p<0.001$. Total RSS Total Score (least square mean) decreased by -2.0 from baseline to week 64. The RGI-C Scale (least squares mean score was +2.2 at week 64 also indicating improvement.

The Review Group had a number of concerns relating to the reliability of the clinical effectiveness evidence in the burosumab studies; (i) the benefits of burosumab in patients aged over 12 years of age until growth plate closure have not been established (ii) it is unclear how generalisable the results from the burosumab studies are to patients in Ireland being treated for XLH – the relative distribution of disease severity (as defined radiographically) in patients with XLH in Ireland may not be the same (or as severe) as the population in the clinical trial programme. This is because radiographic severity is often a result of poor treatment with conventional therapy, which happens infrequently in Ireland and (iii) XLH is a chronic lifelong condition however data on the impact of burosumab on the long-term consequences of XLH are not available.

2. Safety of burosumab

Safety data for CL201 and CL205 was available to 64 weeks. There were no deaths or discontinuations in subjects receiving burosumab over this time. The most common adverse drug reactions reported were injection site reactions (57%). Other adverse drug reactions reported included headache (54%), pain in extremity (42%), vitamin D decreased (28%), rash (23%), toothache (19%), tooth abscess (14%), myalgia (14%) and dizziness (11%). The

treatment emergent adverse events reported in study CL301 were consistent with those identified in the phase 2 studies.

3. Cost effectiveness of burosumab

The cost-effectiveness of burosumab versus conventional therapy was evaluated in a cost-utility analysis. The model was a five state discrete time Markov model consisting of four health states based on rickets severity (healed (RSS = 0), mild (RSS = 0.5 or 1.0), moderate (RSS = 1.5 or 2.0), and severe (RSS ≥2.5)) i.e. higher scores indicating more severe radiographic disease, and the death state.

Transitions between the four health states were informed by data from the burosumab clinical trials and chart review studies, with treatment dependent transition probabilities. Patients continued to transition between health states until age 18 years, at which point they were assumed to remain in the same health state for the rest of the model time horizon or until death. Transition probabilities for burosumab are based on observed transitions from studies CL205 and CL201 every two week dosing regimen arm, and the burosumab arm of CL301. Transition probabilities for conventional therapy are informed by the control arm of CL301 and the UK Chart Review data. Naïve pooling was used to combine the transition matrices generated from the separate studies into treatment specific transition matrices for use in the economic model. The Applicant continued to apply transition probabilities for burosumab until age 18 years (which implies continued improvement for two to four years after cessation of therapy). The Applicant also proposed that treatment with burosumab during childhood would have a treatment effect that persisted into adulthood.

A vignette study was used to estimate utility values for children with XLH. Utility values were elicited from UK-based clinicians (n=7) who valued the health states using the UK EQ-5D 5L, and were subsequently cross-walked to the UK EQ-5D 3L values. An additional elicitation study was undertaken to estimate utility values in individuals aged 18 years with XLH. These vignettes were presented to clinicians experienced with XLH in adults (n=5) and scored using the EQ-5D 5L instrument. The same clinicians were subsequently asked to imagine the health state of the same individual at the ages of 40 and 60 years, and again score this using the EQ-5D 5L instrument, and were subsequently cross-walked to the UK EQ-5D 3L values.

Costs included in the model were subcategorised by treatment costs (both for burosumab and conventional therapy) and health state costs. Health state costs were further subcategorised by surveillance costs, drug costs (for adults only), pain and mobility costs and orthopaedic intervention costs. A discount rate of 4% was applied to costs and health outcomes.

The Review Group had concerns with the approaches and assumptions used by the Applicant in their economic model, including the baseline health state distribution (of disease severity) in the modelled population, the methods used to estimate the transition probability matrices for burosumab, the assumption of lifelong treatment effects for burosumab, as well as the source and methods used to estimate the utilities.

Results

Given the concerns in relation to the assumptions used to model the cost effectiveness, the Review Group applied alternative assumptions to derive an adjusted base case. Choosing an alternate baseline health state distribution; applying treatment cessation at age 15 years (females) and 17 (males), which the Review Group considered was a more accurate reflection of growth plate closure, and hence true stopping age that would be expected in clinical practice; applying a treatment waning effect following cessation of therapy and a treatment cost for burosumab based on the average dose that was used in the trials.

The NCPE Review Group adjusted deterministic ICERs (Table 1) and the Applicant base case deterministic ICERs (Table 2) are shown.

Table 1: NCPE Review Group adjusted base case analysis*

Treatment	***Incremental Costs (€)***	***Incremental QALYs***	***ICER (€ per QALY)***
Conventional therapy			
Burosumab	2,682,568	4.5	662,746

QALY: Quality adjusted life year; **ICER:** Incremental Cost Effectiveness Ratio

*A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded, and so calculations will not be directly replicable.

Table 2: Applicant base case analysis* ^

Treatment	*Incremental Costs (€)*	*Incremental QALYs*	*ICER (€ per QALY)*
Conventional therapy			
Burosumab	1,886,940	5.3	355,780

QALY: Quality adjusted life year; **ICER:** Incremental Cost Effectiveness Ratio. Note that cell referencing errors made in the Applicant's original submission have been corrected for both costs.
*A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded, and so calculations will not be directly replicable.
^Note: The Applicant base case did not include the 8% wholesale margin on the price to wholesaler of burosumab.

A probabilistic analysis of the NCPE Review Group adjusted base case, resulted in an ICER of €847,534 per QALY. This is not reflective of the deterministic ICER, indicating much uncertainty in the cost effectiveness outputs. There was a 0% probability of cost effectiveness at €45,000 per QALY and €20,000 per QALY thresholds using the NCPE adjusted base case.

4. Budget impact of burosumab

The price to wholesaler for burosumab is €3,385.54, €6,770.75 and €10,156.29 for the 10mg/ml, 20mg/ml and 30mg/ml packs respectively (with each pack containing one vial). Burosumab dosing is weight-based and applies to a broad age (and therefore expected weight) range. The recommended starting dose is 0.8 mg/kg of body weight given every two weeks. The maximum dose is 90mg. All doses should be rounded to the nearest 10mg. The Review Group based the cost of burosumab on the weighted average dose used in studies CL201, CL205 and CL301. As burosumab uses weight-based dosing and may be administered to a range of ages under the licensed indication, the average cost used in the budget impact analysis was based on the average expected cost for patients aged one to 17 years inclusive. The Applicant proposed that there will be nine to 16 patients aged between one to 17 years living with XLH in Ireland, all of whom will be eligible for treatment with burosumab. The NCPE Review Group revised these estimates upwards to approximately 25 patients per year, based on clinical opinion in Ireland. The Applicant estimated a gross drug budget impact for

burosumab of €17.4 million (inclusive of VAT) cumulative over five years (based on a prevalent population of approximately 16 patients per year). The cost estimates presented by the Applicant were subject to a number of limitations. The Review Group made a number of changes to the Applicants model including increasing the eligible population, increasing the market share uptake of burosumab, applying a revised cost for burosumab based on reimbursement on the High Tech Drug Arrangement and a maintenance dose based on a weighted average dose used in studies CL201, CL205 and CL301. With these amendments included, the Review Group estimated the gross drug budget impact to be €6.6 million in year one, rising to €7.8 million in year five, giving a five-year cumulative total of €37.9 million (inclusive of VAT). When wholesale mark-up is excluded, the gross budget impact is €35.1 million (inclusive of VAT).

Drug costs associated with conventional therapy were estimated at €1,114 per patient per year. When the net drug budget impact was re-calculated using the Review Group's adjusted base case parameters, the net drug budget impact of burosumab was €37.8 million over 5 years. The corresponding estimate when wholesale mark-up is excluded is €34.9 (inclusive of VAT) million.

The Applicant did not consider any additional costs or cost offsets as part of the budget impact analyses.

5. State if any patient submissions were received, and name submitting organisations.

Patient submissions were received during the course of this assessment.

6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that burosumab (Crysvita®) not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.