NCPE Assessment

Technical Summary

Burosumab (Crysvita®)

23005

31 July 2024

Applicant: Kyowa Kirin

Burosumab for the treatment of adults, with XLH, who have persistent symptoms despite conventional therapies or who are intolerant of conventional therapies.

This is a subpopulation of the licensed adult population.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (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, for this indication*.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Kyowa Kirin) Health Technology Assessment of Burosumab (Crysvita®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative 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.

Summary

In September 2023, Kyowa Kirin submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of burosumab (Crysvita®) for the treatment of adults with X-linked hypophosphataemia (XLH), who have persistent symptoms despite conventional therapies or who are intolerant of conventional therapies. This is a subpopulation of the licensed adult population. Clinical opinion, to the Review Group, indicates that this subpopulation is aligned with the adult population who are likely to be considered for treatment, in Ireland. Burosumab is currently reimbursed, in Ireland, for the treatment 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 monoclonal antibody (IgG1) that binds to and inhibits the activity of FGF23, resulting in tubular reabsorption of phosphate from the kidney and increases in serum concentration of 1,25 dihydroxy-vitamin D. Burosumab is administered at a subcutaneous (SC) dose of 1mg/kg of body weight, rounded up to the nearest 10mg, once every four weeks. There is potential for life-long therapy with burosumab, provided that clinical benefit continues and the drug is tolerated. Reimbursement is sought in the hospital setting. The Summary of Product Characteristics (SmPC) states self-administration could be considered once no immediate dose modifications are anticipated and training in injection technique has been provided.

1. Comparative effectiveness of burosumab

The efficacy and safety of burosumab was investigated in the completed phase three CL303 trial and open-label extension study BUR02. CL303 was a randomised, double-blind, 24-week placebo-controlled study, with open-label continuation (Week 24 to 48) and extension (Week 48 to 96) periods to assess the efficacy and safety of burosumab in adults with XLH. Participants were randomised 1:1 to SC burosumab or placebo. The study included adult patients with XLH who had a Brief Pain Inventory worst pain score of four or more, indicating moderate to severe pain. All study participants concurrently received best supportive care (BSC), which could include pain medication, rescue medication, physical therapy, and occupational therapy. The use of conventional standard of care (SoC) treatments (i.e.

vitamin D and phosphate supplementation) was not permitted and a wash out period of at least two weeks was required prior to trial enrolment. The primary endpoint, the proportion of participants attaining a mean serum phosphate concentration above the lower limit of normal (LLN), was met at Week 24 (94.1% in the burosumab arm vs 7.6% in the placebo arm; p<0.0001). After Week 24, all participants entered an open-label treatment continuation period (Weeks 24 to 48), during which all participants received burosumab. Based on clinical opinion, obtained by the Review Group, it is uncertain if normalisation of serum phosphate concentration translates into improvements in clinically meaningful outcomes. Other endpoints, such as the number of active fractures/pseudofractures and six-minute walking test outcomes were suggestive of a clinical benefit. As these are exploratory endpoints, it remains uncertain whether burosumab is associated with a non-fracture related morbidity benefit. Furthermore, due to lack of a comparator arm beyond Week 24, it remains uncertain whether burosumab will prevent new fractures. The Applicant proposed a mortality benefit with burosumab due to avoidance of new fractures. However, this assumption was not substantiated by the clinical evidence. A number of potential biases in the conduct of CL303 were noted including the inclusion of WOMAC scores (physical function and stiffness) as key secondary endpoints after the Week 24 analysis, the open-label nature of the trial and imbalances in pain across both arms at baseline. These issues may have biased patient-reported outcomes in favour of burosumab.
Following an open-label treatment extension period (Weeks 48 to 96), European-based participants had the option to take part in the 48-week, phase three b, multicentre, open-label extension study, BUR02. The study design of BUR02 broadly aligned with the treatment continuation period of CL303. Serum phosphate was maintained within normal ranges between Weeks 48 and 96. Evidence from Week 24 to 48 of CL303 and from BUR02 indicate that continuous use with burosumab is required to maintain a clinical benefit.

2. Safety of burosumab

The safety profile of burosumab, when used in adults, is considered to be in line with the known safety profile in the child and adolescent population, apart from a potentially higher risk of hypophosphatemia (reported in about 10% of participants in the adult safety database). During the placebo-controlled period of CL303, reported rates of treatment-

emergent adverse events (TEAEs) were comparable in both study arms (94% in the burosumab arm vs 92% in the placebo arm). The proportion of serious adverse events (AEs) was the same in each treatment arm (3%), and none were deemed related to the study drug. The proportion of participants experiencing a Grade 3 or 4 TEAE were similar across both arms (12.1% vs 11.8%). TEAEs reported more commonly in the burosumab arm compared to the placebo arm included back pain (14% vs 6%), tooth abscess (13% vs 8%), restless legs (12% vs 8%), decreased Vitamin D serum concentration (12% vs 5%), and dizziness (10% vs 6%).

3. Cost effectiveness of burosumab

Methods

The analysis was conducted from the perspective of the HSE in Ireland. The cost-effectiveness model (CEM) only considered a subpopulation of the licensed adult population; adult patients with XLH who have persistent symptoms despite conventional treatment or who are intolerant of conventional therapies. Model population characteristics were based on the Europe-based trial population of CL303. Participants in CL303 had to have moderate to severe pain, however no other evidence of symptoms were specified in the inclusion criteria. The Review Group note there is no clinical evidence regarding the efficacy of burosumab in the broader adult population with XLH, including those who are asymptomatic. As such, it is not possible to evaluate the clinical or cost effectiveness of burosumab in the fully licensed adult population. The Applicant considered BSC, excluding conventional SoC treatments (i.e. vitamin D and phosphate supplementation) to be the relevant comparator. Direct evidence was derived from CL303; the placebo arm of which was considered to be BSC (excluding conventional SoC treatments). The model comprises several interlinked cohort-state transition models which track overall survival, treatment status (on or off treatment) and morbidities experienced by patients in the 'alive' health states. The treatment effects captured by the CEM were serum phosphate normalisation, defined as the proportion of participants who achieved a mean serum phosphate concentration above the LLN. The key efficacy inputs, to the model, are reductions in the incidence of morbidities (assumed to be fractures only in the base case) and mortality. These reductions are assumed to apply to the incremental proportion of participants in the burosumab arm who attained serum phosphate normalisation at Week 24, relative to the

BSC arm. The Applicant assumed that 100% of participants treated with burosumab attained serum phosphate normalisation (as opposed to 94.1% at Week 24 in CL303). The Review Group therefore considered this to be an overestimate and instead used data from CL303 in the NCPE adjusted base case. The Applicant assumed that a 100% reduction in XLH-related fractures is applicable to all participants who achieve serum phosphate normalisation. In the absence of long-term comparative data, the Review Group consider an assumption of a 50% reduction in fracture incidence rate compared with BSC, derived using CL303 data at Week 24, to be more appropriate. Given the limited data available, the Review Group consider the incident fracture rate to be subject to considerable uncertainty.

Treatment benefits, with regards to pain and stiffness, are assumed to be captured through WOMAC scores. WOMAC scores were mapped to the EQ-5D-3L to generate utility values. Baseline utility in the CEM was estimated via a regression analysis of the pooled baseline utility in CL303. The incremental benefit of burosumab was estimated as the change from baseline in utility, adjusted by placebo utility values. Disutilities due to fractures were accounted for in the CEM.

The Review Group identified a number of limitations in the Applicant's CEM, which were addressed through changes in the NCPE-adjusted base case including; use of data from CL303 up to Week 96, removal of subsequent disutilities in the year after incident fracture, and removal of the stopping rule based on an improvement in WOMAC score.

Results

The results of the Applicant's base case deterministic cost-effectiveness analysis are presented in Table 1. Results of the NCPE-adjusted base case are presented in Table 2. The probability of cost-effectiveness of burosumab is presented in Table 3.

Table 1: Applicant base case incremental cost-effectiveness results [a,b,c]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
BSC[d]	10,383	7.41			
Burosumab	2,596,108	10.00	2,585,725	2.59	999,735

BSC: Best Supportive Care; **QALY:** Quality Adjusted Life Year

[a] Corresponding probabilistic ICER using 2,500 iterations = €1,151,147/QALY. Figures in the table are rounded, and so calculations may not be directly replicable.

[b] There is a CIC PAS for burosumab, not included in this table.
[c] Costs and outcomes are discounted at 4%.
[d] BSC excluding standard of care conventional treatments

Table 21: NCPE adjusted base case incremental cost-effectiveness results [a,b,c]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
BSC[d]	10,680	7.60	-	-	-
Burosumab	2,899,148	9.22	2,888,467	1.63	1,777,200

BSC: Best Supportive Care; **QALY:** Quality Adjusted Life Year; **ICER**: incremental cost-effectiveness ratio.
[a] Corresponding probabilistic ICER using 2,500 iterations = €1,790,254/QALY. Figures in the table are rounded, and so calculations may not be directly replicable
[b] There is a CIC PAS for burosumab, not included in this table.
[c] Costs and outcomes are discounted at 4%.
[d] BSC excluding standard of care conventional treatments

Table 3: Probability of cost effectiveness for burosumab vs BSC [a]

	Probability of cost effectiveness	
Threshold (€/QALY)	Applicant base case	NCPE adjusted base case
20,000	0%	0%
45,000	0%	0%

BSC: Best Supportive Care; **QALY:** Quality Adjusted Life Year **ICER**: incremental cost-effectiveness ratio.
[a] Results based on probabilistic analysis using 2,500 iterations

When compared to BSC (excluding conventional SoC treatments), a total reduction of approximately 97.78% (89.25% discount and 8.5% Framework Agreement rebate) in the price to wholesaler is required to achieve an ICER of €45,000/QALY. The Review Group highlight that a number of assumptions regarding treatment effects made by the Applicant are not evidence based. While some variation around these parameters is included in the probabilistic sensitivity analyses this does not fully reflect the uncertainty associated with these parameters and assumptions.

Additional scenario analyses were conducted by the NCPE, in which the incremental utility benefit associated with burosumab was removed (ICER: €17,665,292/QALY), where only utility data up to Week 24 of CL303 were used (ICER: €2,907,751/QALY), the mortality benefit of burosumab was removed (ICER: €1,931,596/QALY), and mean dose of burosumab was rounded to the nearest 10mg (i.e. 70mg) once every four weeks (ICER: €1,907,105/QALY).

4. Budget impact of burosumab

The price-to-wholesaler of the three different strengths of burosumab are: €3,011.99

(10mg/ml), €5,958.18 (20mg/ml) and €8,929.66 (30mg/ml). The Review Group noted that the approach taken to costing in the budget impact model (BIM) was inconsistent with CEM, in that all patients were assumed to receive 70mg once every four weeks. Furthermore, 10mg and 30mg vials were used in annual treatment course cost calculations. In the BIM, the annual treatment course cost of burosumab is estimated to be €311,736 (€249,117 excluding VAT).

Many of the budget-impact model inputs are very uncertain and there is considerable uncertainty associated with the budget impact estimates. Under the Applicant's market share and discontinuation rate assumptions, the number of patients treated with burosumab is estimated to be nine in Year One, rising to 11 in Year Five. The Review Group highlight that this submission considers that burosumab will only be used in adult patients with XLH who have persistent symptoms despite conventional SoC treatments; thus, representing a subpopulation of the fully licenced adult population. Clinical opinion, to the Review Group, indicates that this subpopulation is aligned with the adult population, who will be considered for treatment, in Ireland. The cumulative five-year gross drug budget impact of burosumab was estimated, by the Applicant, to be €15.12 million (including VAT). There are no drug costs associated with BSC; thus, the net drug-budget impact is equivalent to the gross drug-budget impact. The Review Group conducted a scenario whereby the drug was available for the licensed adult population the resulting net drug budget impact was about €30.23 million (including VAT). All budget impact estimations are highly uncertain.

5. Patient Organisation Submission

No patient organisation submissions were received during the course of the assessment

6. Conclusion

The NCPE recommends that burosumab not be considered for reimbursement*.

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