An addendum to this Public Summary Document has been included at the end of the document.

7.01 BUROSUMAB,

Injection 10 mg in 1 mL, Injection 20 mg in 1 mL, Injection 30 mg in 1 mL

Crysvita®

Kyowa Kirin Australia Pty Ltd®

1 Purpose of submission

1.1 The Standard Re-Entry resubmission requested a Section 100 – Highly Specialised Drugs Program listing for burosumab, for the treatment of paediatric and adult patients with X-linked hypophosphataemia (XLH). Listing was requested on the basis of cost-utility analyses versus conventional therapy (oral phosphorus and active vitamin D (calcitriol)). This is the second submission for burosumab, the previous submission was in March 2021 and was for treatment of XLH in children only.

1.2 At the March 2021 meeting, the PBAC had considered an age agnostic restriction to be more appropriate, noting likely continued benefits of burosumab in adults in terms of normalisation of serum phosphate levels, improved physical functioning, fracture healing and reduced stiffness. The PBAC also noted the strong consumer support for an age agnostic listing, the importance of equity of access and that the effects of XLH are life-long.

1.3 Given this, the resubmission amended the requested restriction from its March 2021 submission to include use in adults. In addition to an updated clinical and economic evaluation of burosumab in children, new clinical data and a modelled economic evaluation were also presented for adults.

Table 1: Key components of the clinical issue addressed by the resubmission

Component	Description
Population	Patients with a diagnosis of XLH confirmed by specified genetic and/or clinical/laboratory criteria
Intervention	In patients <18 years of age • BUR 0.8 mg/kg (rounded to next 10 mg) with upwards/downwards titration according to the label, administered every two weeks by subcutaneous injection; • Treatment by paediatric endocrinologist or paediatric nephrologist and administration by a healthcare professional. In patients ≥18 years of age • BUR 1.0 mg/kg (rounded to next 10 mg) with upwards/downwards titration according to the label, administered every four weeks by subcutaneous injection; • Treatment by an endocrinologist or nephrologist and administration by a healthcare professional.
Comparator	In patients <18 years of age • Conventional therapy comprising multiple daily oral doses of phosphorus and calcitriol In patients ≥18 years of age • A mix of conventional therapy (as above) and routine symptomatic management
Outcomes	In patients <18 years of age • Pharmacodynamic: serum phosphorus, TmP/GFR, 1,25(OH)2D, ALP, TRP and others • Clinical: Rickets severity as measured by RSS and RGI-C and growth • Functional: 6MWT • Patient reported: PROMIS, SF-10 • Safety: Incidence and severity of AEs • Extrapolated: utilities, rates of surgery, other healthcare utilisation In patients ≥18 years of age • Pharmacodynamic: serum phosphorus, TmP/GFR, 1,25(OH)2D, ALP, TRP, P1NP, CTx • Clinical: Healing of fractures and pseudofractures • Functional: 6MWT, TUG • Patient reported: WOMAC, BPI, BFI
Clinical claim	In children with XLH, BUR is superior in terms of effectiveness and safety compared to conventional therapy. In adults with XLH, BUR superior in effectiveness and inferior (acceptable) in safety compared to placebo (and probably conventional therapy).

Blue shading represents information previously considered by the PBAC.
Source: Table 1-1, p19 of the resubmission.
AE=adverse event; ALP=alkaline phosphatase; BFI=Brief Fatigue Inventory, BPI=Brief Pain Inventory; BUR=burosumab; CTx=Cross-linked C-terminal Telopeptide of Type 1 Collagen; P1NP=Pro-collagen 1 Intact N-terminal Propetide; PROMIS=Patient-Reported Outcomes Measurement Information System; RGI-C=Radiographic Global Impression of Change; RSS=Rickets Severity Score; SF-10=SF-10 Health Survey for Children; TmP/GFR=ratio of renal tubular maximum reabsorption rate of phosphate (TmP) to glomerular filtration rate (GFR); TPR=Tubular phosphate reabsorption; TUG=Timed Up and Go; WOMAC=Western Ontario & McMaster University Osteoarthritis Index; XLH=X-linked hypophosphataemia; 1,25(OH)2D=1,25-dihydroxyvitamin D; 6MWT=six-minute walk test

2 Background

Registration status

2.1 Burosumab received approval from the TGA on 10 September 2021 for the following indication:

> "CRYSVITA (burosumab) is indicated for the treatment of X-linked hypophosphataemia (XLH) in adults, adolescents and children 1 year of age or older."

Previous PBAC consideration

2.2 Burosumab was previously considered by the PBAC in March 2021. Table 2 summarises the key concerns identified in the March 2021 submission and the response taken by the resubmission.

Table 2: Summary of key matters of concern and how the resubmission addressed them

Component	March 2021	March 2022 (current resubmission)
Restriction	The PBAC considered an age agnostic listing for BUR to be more appropriate. The PBAC also considered that eligibility criteria should include more clinically based criteria such as serum phosphate levels, radiographic evidence of rickets and confirmation of a PHEX pathogenic variant. The continuation criteria should also reflect the maintained effects of BUR (para 7.5, burosumab Public Summary Document [PSD] March 2021). A clinical expert consultation (CEC) meeting was convened by the PBAC in May 2021 to discuss aspects of the proposed restrictions for burosumab.	An amended age agnostic listing was requested by the resubmission. The requested restriction was also amended to reflect outcomes of the CEC meeting including clinically defined initiation and continuation criteria. A continuation criterion considered appropriate at the CEC of "normalisation of serum phosphate levels" was amended to "normalisation or greater than 30% improvement from pre-treatment baseline in serum phosphate levels". This may not be appropriate.
Clinical evidence & clinical claim	The PBAC noted (para 7.4 and 7.5, burosumab PSD March 2021): • the population in the paediatric trials (i.e. children aged 1 to 12 years) did not match the population in the proposed restriction (i.e. children up to the age of 18 years). • a relevant trial, KRN23-003 was inappropriately excluded as the study treatment was via self-administration (which the PBAC considered would be important for equity of access). • a number of clinical trials were available that evaluated the effects of BUR in adults. The PBAC considered that for children aged 1 to 12 years, BUR was superior in terms of effectiveness compared to conventional therapy, however no clinical trial data was presented for children aged 13 to 17 years and long term effects were unknown given the limited trial data. BUR also has a different safety profile compared to conventional therapy with more appreciable short-term side-effects (paras 7.8 and 7.9, burosumab PSD March 2021).	The same clinical data was presented for the paediatric population but KRN23-003 was included as additional supportive evidence. Data from KRN23-003 was presented by the evaluators in the March 2021 Commentary. New data in the adult population was presented, based on one trial (CL303), comparing BUR to placebo and 6 single-arm studies as supportive evidence. The clinical claim was unchanged for paediatric patients with XLH. In adult patients, the resubmission claimed BUR to be superior in terms of effectiveness and inferior but acceptable in terms of safety compared to comparators. No additional data was presented for patients aged 13 to 17 years.

Component	March 2021	March 2022 (current resubmission)
Economic evaluation	The PBAC considered (paras 7.11, 7.14, burosumab PSD March 2021) that: • a price reduction would be required to address the numerous uncertainties in the model and to achieve a reasonable ICER in the whole XLH population • RSS was unlikely to capture all relevant outcomes and the inclusion of a 'healed' state was inconsistent with trial-based patient reported outcomes • average dose was modelled as 0.86 mg/kg, which PBAC considered was likely to be low • annualised transition probabilities were constant to age 18 years, with stabilisation of disease severity from age 18, resulting in nearly all BUR patients entering the 'healed' state by Year 10 and continuing to accrue these benefits until death • there was limited effectiveness data • cost of harms were not included The PBAC however noted that consumer input was supportive of BUR treatment in adults as well as children, but that potential benefits to adults would need to be better quantified (para 7.2, burosumab PSD March 2021).	The economic evaluation was updated in the following ways: • a [redacted]% reduction in the requested effective prices for BUR compared to March 2021 submission. • RSS remained the main outcome, but a small survival benefit was also assumed for BUR versus conventional therapy. • mean dose for children was increased to 0.91 mg/kg based on unpublished data from the North American Disease Monitoring Program. This was still lower than the mean dose received in the Early Access Program (EAP) of 1.05 mg/kg and the maximum dose in the draft product information (2 mg/kg). • extrapolation of the transition probabilities remained unchanged, but the resubmission did include the cost of BUR treatment into adulthood, with utilisation decreasing from 100% (80% from age 18 years, 60% from age 20 years, 50% from age 30-57 years). • time horizon reduced from 100 years in the March 2021 submission to 50 years in the resubmission. • a new cost-effectiveness analysis based on treatment in adults, focused on morbidity events was presented.
Financial estimates & risk share	The PBAC considered (paras 7.12, 7.16 burosumab PSD March 2021), that: • the financial estimates in paediatrics were likely underestimated due to uncertainty in the dose, uptake rates would be higher in the initial years of listing due to more older and heavier prevalent patients likely being treated initially, absence of treatment for AEs and potentially more patients would be identified if BUR was listed on the PBS and PHEX mutation testing was more readily available. The PBAC considered that a resubmission should inform utilisation in adults and children. An RSA consisted of fixed expenditure caps, beyond which rebates were applied, would also be necessary to mitigate risk relating to the financial impact of listing BUR (para 7.15, burosumab PSD March 2021).	The financial estimates were revised incorporating prevalence of XLH in paediatrics and adults, lower effective price, dose regimen from North American Disease Monitoring Program and uptake rates for paediatrics and adults. The resubmission included an RSA and proposed to reimburse the Australian government [redacted]% of any expenditure on BUR, over and above the annual financial caps, which would be calculated based on the resubmission's base case assumptions of eligibility, uptake, and utilisation.

Source: Compiled during the evaluation.
AE=adverse event; BUR=burosumab; CEC=clinical expert consultation; EAP=early access program; PHEX=phosphate-regulating endopeptidase homolog; RSA=risk sharing arrangement; SPA=special pricing arrangement; XLH=X-linked hypophosphataemia

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

3.1 The requested listing and suggested wording for the restriction as proposed by the Secretariat (additions are in italics, deletions in strikethrough) is presented below.

Table 3: Essential elements of the requested listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity		Proprietary name and manufacturer
Initial / Continuing / Grandfathered				*Published:*	*Effective:*	
BUROSUMAB 10 mg in 1 mL^	2	2	0	$15,768.00 (public) $15,815.78 (private)	$[redacted] (public) $[redacted] (private)	Crysvita® Kyowa Kirin Australia Pty Ltd
BUROSUMAB 20 mg in 1 mL^	2	2	0	$31,536.00 (public) $31,583.78 (private)	$[redacted] (public) $[redacted] (private)	
BUROSUMAB 30 mg in 1 mL^	2	2	0	$47,304.00 (public) $47,351.78 (private)	$[redacted] (public) $[redacted] (private)	

Blue shading represents information previously considered by the PBAC.

Source: Tables 1-3 to 1-6, pp30-33 of the resubmission.

^ *Each of the three strengths will be provided in 1 mL of deliverable volume, with differing concentrations: 10 mg/mL, 20 mg/mL and 30 mg/mL. However, the capacity of the vials in which all three strengths/concentrations will be provided is 5 mL.*

Category / program: ~~Section 100 (Highly Specialised Drugs Program)~~ *Section 85 General Listing*
Prescriber type: ☒ Medical Practitioners
Restriction type: ☒ ~~Authority Required - In Writing (Full Assessment – Pended)~~ ☒ *Authority Required – telephone/online PBS Authorities system*
Episodicity: ~~Chronic~~ [blank]
Severity: ~~NA~~ [blank]
Condition: X-linked hypophosphataemia
PBS Indication: X-linked hypophosphataemia
Treatment phase: Initial
Clinical criteria:
Patient must have *a documented* confirmation of PHEX pathogenic variant ~~documented in their medical records~~; OR
Patient must have a diagnosis of X-Linked hypophosphataemia ~~confirmed, and documented in their medical records,~~ by the presence of all of the following: (i) ~~hypophosphataemia~~ *a serum phosphate concentration below the age adjusted lower limit of normal*; (ii) current or historical (for those with growth plate fusion) radiographic *X-ray* evidence of rickets; (iii) elevated (or inappropriately normal) serum or plasma FGF-23 levels *of above the mean of the assay-specific reference range*; (iv) renal phosphate wasting *demonstrated by a ratio of tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) according to age specific normal ranges using the second morning urine void and paired serum sample measuring phosphate and creatinine*
Treatment criteria:
Patient must be treated by one of the following specialists: (i) paediatric endocrinologist, (ii) paediatric nephrologist, (iii) endocrinologist, or (iv) nephrologist
Prescriber instructions:
~~For the purposes of administering this restriction hypophosphataemia is defined as a serum phosphate concentration below the age adjusted lower limit of normal~~
~~For the purposes of administering this restriction radiographic evidence of rickets requires a x-ray demonstrating evidence of rickets~~
~~For the purposes of administering this restriction an elevated (or inappropriately normal) serum or plasma FGF-23 levels are defined as above the mean of the assay-specific reference range~~

~~For the purposes of administering this restriction renal phosphate wasting is the ratio of tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) according to age specific normal ranges using ideally the second morning urine void and paired serum sample measuring phosphate and creatinine~~
~~At the time of authority application, medical practitioners must request the appropriate number of vials of appropriate strength*(s)* to provide sufficient drug, based on the weight of the patient, for *two* administrations. A separate authority prescription form must be completed for each strength requested. Up to a maximum of 3 items will be authorised for any 1 administration.~~
~~Applications for authorisation of initial treatment must be in writing and must include:~~ ~~(a) A completed authority prescription form; and~~ ~~(b) A completed PBS authority application form relevant to the indication and treatment phase (the latest version is located at the website mentioned in the administrative note.~~
Administrative advice: Special Pricing Arrangements apply
~~Note~~ ~~Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).~~ ~~Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au~~ ~~Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos~~ ~~Or mailed to:~~ ~~Services Australia~~ ~~Complex Drugs~~ ~~Reply Paid 9826~~ ~~HOBART TAS 7001~~
Note *Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).*

Category / program: ~~Section 100 (Highly Specialised Drugs Program)~~ *Section 85 General Listing*
Prescriber type: ☒Medical Practitioners
Restriction type: ☒ ~~Authority Required - In Writing (Full Assessment – Pended)~~ ☒ *Authority Required – telephone/online PBS Authorities system*
Episodicity: ~~Chronic~~ [blank]
Severity: ~~NA~~ [blank]
Condition: X-linked hypophosphataemia
PBS Indication: X-linked hypophosphataemia
Treatment phase: Continuing
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must have ~~demonstrated an adequate response to this drug for the treatment of this condition~~ achieved ~~(i)~~ normalisation in serum phosphate levels~~; or (ii) a greater than 30% improvement from pre-treatment baseline in serum phosphate levels~~
AND
Clinical criteria
Patient must have radiographical evidence of stabilisation or improvement in rickets in patients without growth plate fusion

Treatment criteria:
Patient must be treated by one of the following specialists: (i) paediatric endocrinologist, (ii) paediatric nephrologist, (iii) endocrinologist, or (iv) nephrologist
Prescriber instructions:
~~For the purposes of administering this restriction, an adequate response to treatment with burosumab includes (i) normalisation or greater than 30% improvement from pre-treatment baseline in serum phosphate levels; and (ii) radiological evidence of stabilization or improvement in rickets in patients without growth plate fusion.~~
Where adequate response to treatment with burosumab cannot be demonstrated, evidence that consideration of continuing therapy has been determined to be clinically required by a second specialist physician with expertise in the treatment of X-linked hypophosphataemia.
~~At the time of authority application, medical practitioners must request the appropriate number of vials of appropriate strength(s) to provide sufficient drug, based on the weight of the patient, adequate for one month's supply. A separate authority prescription form must be completed for each strength requested. Up to a maximum of 3 items will be authorised for any 1 administration.~~
~~Applications for authorisation of initial treatment must be in writing and must include:~~ ~~(a) A completed authority prescription form; and~~ ~~(b) A completed PBS authority application form relevant to the indication and treatment phase (the latest version is located at the website mentioned in the administrative note.~~
Administrative advice: Special Pricing Arrangements apply
~~Note~~ ~~Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).~~ ~~Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au~~ ~~Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos~~ ~~Or mailed to:~~ ~~Services Australia~~ ~~Complex Drugs~~ ~~Reply Paid 9826~~ ~~HOBART TAS 7001~~
Note *Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).*

Category / program: ~~Section 100 (Highly Specialised Drugs Program)~~ *Section 85 General Listing*
Prescriber type: ☒Medical Practitioners
Restriction type: ☒ ~~Authority Required - In Writing (Full Assessment – Pended)~~ ☒ *Authority Required – telephone/online PBS Authorities system*
Episodicity: ~~Chronic~~ [blank]
Severity: ~~NA~~ [blank]
Condition: X-linked hypophosphataemia
PBS Indication: X-linked hypophosphataemia
Treatment phase: Grandfather
Clinical criteria:

Patient must have *a documented* confirmation of PHEX pathogenic variant ~~documented in their medical records~~; OR
Patient must have a *confirmed* diagnosis of X-Linked hypophosphataemia ~~confirmed, and documented in their medical records,~~ by the presence of all of the following: (i) ~~hypophosphataemia~~ *a serum phosphate concentration below the age adjusted lower limit of normal*; (ii) current or historical (for those with growth plate fusion) radiographic evidence of rickets; (iii) elevated (or inappropriately normal) serum or plasma FGF-23 levels *of above the mean of the assay-specific reference range*; (iv) renal phosphate wasting *demonstrated by a ratio of tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) according to age specific normal ranges using the second morning urine void and paired serum sample measuring phosphate and creatinine*
AND
Clinical criteria:
Patient must have demonstrated an adequate response to non-PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [listing date]
~~*AND*~~
~~**Clinical criteria:**~~
~~Patient may only qualify under this treatment phase once~~
Treatment criteria:
Patient must be treated by one of the following specialists: (i) paediatric endocrinologist, (ii) paediatric nephrologist, (iii) endocrinologist, or (iv) nephrologist
Prescriber instructions:
~~For the purposes of administering this restriction hypophosphataemia is defined as a serum phosphate concentration below the age adjusted lower limit of normal~~
~~For the purposes of administering this restriction radiographic evidence of rickets requires a x-ray demonstrating evidence of rickets~~
~~For the purposes of administering this restriction an elevated (or inappropriately normal) serum or plasma FGF-23 levels are defined as above the mean of the assay-specific reference range~~
~~For the purposes of administering this restriction renal phosphate wasting is the ratio of tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) according to age specific normal ranges using ideally the second morning urine void and paired serum sample measuring phosphate and creatinine~~
~~At the time of authority application, medical practitioners must request the appropriate number of vials of appropriate strength*(s)* to provide sufficient drug, based on the weight of the patient, for *two* administrations. A separate authority prescription form must be completed for each strength requested. Up to a maximum of 3 items will be authorised for any 1 administration.~~
~~Applications for authorisation of initial treatment must be in writing and must include:~~ ~~(a) A completed authority prescription form; and~~ ~~(b) A completed PBS authority application form relevant to the indication and treatment phase (the latest version is located at the website mentioned in the administrative note.~~
Administrative advice: Special Pricing Arrangements apply
Administrative advice: *This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria*
~~Note~~ ~~Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).~~ ~~Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au~~ ~~Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos~~ ~~Or mailed to:~~

~~Services Australia~~ ~~Complex Drugs~~ ~~Reply Paid 9826~~ ~~HOBART TAS 7001~~
Note *Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).*

3.2 The resubmission proposed a reduction in the effective ex-manufacturer prices (AEMPs) of each dose form of burosumab, representing a % reduction on the effective AEMP requested in the March 2021 submission. The pre-PBAC response offered a further % reduction in the effective AEMP.

3.3 The requested restrictions in the resubmission were amended from the March 2021 submission based on the outcomes of the PBAC convened Clinical Expert Consultation (CEC) meeting in May 2021. The revised requested listing was age agnostic. Compared to the March 2021 restrictions more clinically orientated initiation and continuation criteria were proposed. A grandfathering restriction was also requested to allow eligible patients from a burosumab early access program (EAP) to continue treatment on PBS.

3.4 The requested restrictions were consistent with outcomes of the CEC meeting with the exception of a proposal to change one of the continuation criteria from "normalisation of serum phosphate levels" to "normalisation or greater than 30% improvement from pre-treatment baseline in serum phosphate levels". This change may not be appropriate. Given normal range for serum phosphate varies with age, a '≥30% improvement on pre-treatment baseline phosphate levels' may be uninformative for some patients. For example, adolescents and adults who initiated burosumab as paediatric patients would have had their pre-treatment baseline serum phosphate measured many years prior, so referring to historical baselines would not help determine how well these patients are responding to present treatment with burosumab. Therefore, it may be more appropriate to refer to an age-appropriate reference range and allow clinicians to apply judgement. The CEC meeting noted that phosphate levels do commonly decrease when a child is growing and the child 'out-grows' their current burosumab dose. This is an indication that the dose should be increased, not that burosumab has become an ineffective treatment.

3.5 The Pre-Sub-Committee Response (PSCR) stated that the proposed 30% threshold was based on a post-hoc analysis of data from the CL303 study, Brandi 2020[1]. The PSCR

[1] Brandi ML, Wood S, Nixon M, et al. Clinical responses in adult XLH patients not achieving consistent serum phosphate normalisation: A subgroup analysis of a randomised, double-blind, placebo-controlled, Phase III study. ASBMR 2020 Annual Meeting; Sept 11-15, 2020.

also noted that since the resubmission was finalised, an international expert review[2] has been published which provided further pragmatic response criteria, stating "In general, we consider the following to be useful indication of a good response to burosumab therapy in patients with XLH, as has been shown in clinical trials when analysed at the midpoint between doses: a 50% increase from baseline in serum phosphate concentration (even if LLN is not achieved); a 50% decline from baseline in fractional excretion of phosphate; and/or a 50% increase in TmP/GFR. Assessment of total alkaline phosphatase (ALP) in children or bone-specific ALP in adults, can also be used to monitor response." The PSCR stated that either a 30% or 50% improvement would limit the number of instances where a second specialist physician opinion would be required. The ESC noted that the proposed continuation criterion in the restriction applied to all eligible patients (i.e. paediatric and adult); however, the 30% threshold was based on CL303 which enrolled only adults. In addition, the ESC noted that the international expert review highlighted the need to consider age-, and sex-specific reference values when monitoring serum phosphate responses to treatment, including consideration of menopause and puberty influencing target serum levels.

3.6 The requested restrictions did not clearly define when a patient should be assessed for response to burosumab to ascertain eligibility for continued PBS treatment. It was noted that the quantities requested for initiation and continuation therapy, would provide for 1 month of initial treatment and up to 6 months of continuing treatment, but these may be inadequate durations to assess response. Also, as response in paediatric and adult patients are to be measured differently (i.e., based on serum phosphate levels and radiographic evidence of rickets in children versus serum phosphate levels only in adults) different assessment time frames may be necessary for the two populations. It was noted that change in serum phosphate levels was measured between Week 40-64 in CL301 (the main paediatric trial) and at Week 24 in CL303 (the main adult trial). Radiographic evidence of rickets was assessed between Week 40-64 in the paediatric trial only. In clinical practice, all patients on burosumab treatment are likely to require regular serum phosphate monitoring (i.e., every 2 or 4 weeks within the first 3 months of treatment then periodically thereafter) and less frequent radiographic monitoring in children (e.g., 6 months after initiating treatment and every 1 to 2 years to guide treatment adjustment[3,4,5]).

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[2] Aljuraibah F, Bacchetta J, Brandi ML, et al. An expert perspective on phosphate dysregulation with a focus on chronic hypophosphatemia. JBMR. 2021:DOI 10.1002/jbmr.4486

[3] Aljuraibah F, Al Amiri E, Al Dubayee M, et al. 2021. Diagnosis and management of X-linked hypophosphatemia in children and adolescent in the Gulf Cooperation Council countries. Archives of Osteoporosis. 16(1):52.

[4] Rothenbuhler A, Schnabel D, Högler W, Linglart A. 2020. Diagnosis, treatment-monitoring and follow-up of children and adolescents with X-linked hypophosphatemia (XLH). Metabolism. 103:153892. doi: 10.1016/j.metabol.2019.03.009.

[5] Haffner D, Emma F, Eastwood DM, et al. 2019. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. Nat Rev Nephrol. 15(7):435-455.

3.7 The PSCR acknowledged that the resubmission did not formally propose a duration of initial treatment or specify any number of repeats. The PSCR stated that a six-monthly assessment of serum phosphate response was likely appropriate for both paediatric and adult populations, but the radiographic assessment of rickets improvement in children would be more reasonably conducted after 12 months of treatment. Ongoing assessments of response, for continuation of treatment beyond 12 months could reasonably conducted annually, with emphasis on maintenance of improvements in serum phosphate levels and/or rickets severity, as continuous change in these outcomes beyond one year was unlikely.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 XLH is a rare, lifelong and progressive, X-linked inherited disorder characterised by low levels of phosphate in the blood. XLH is caused by mutations on the X chromosome (PHEX) gene. Excess levels of circulating fibroblast growth factor 23 (FGF23) result in reduced renal phosphate reabsorption and decreased production of active vitamin D leading to chronic hypophosphataemia. Clinical manifestations of XLH in children lead to impaired mobility and physical function. Skeletal abnormalities and short stature acquired in childhood become irreversible after the completion of growth. The presence of skeletal deformities along with persistent hypophosphataemia in adulthood drives the ongoing evolution and progression of disease (as bones require phosphate for ongoing development). The population targeted in the resubmission is all patients regardless of age with XLH. Burosumab is expected to improve rickets and growth (height) in children and adolescents with growing skeletons; these effects diminish once growth plates are closed (epiphyseal closure), although there are other benefits of burosumab in adults such as normalisation of serum phosphate levels, improving physical functioning and reducing pain and stiffness.

4.2 Burosumab is a recombinant human monoclonal antibody (immunoglobulin G subclass (IgG1)) that binds to and inhibits the activity of FGF23. By blocking FGF23 activity, there is increased renal tubular reabsorption of phosphate and serum concentration of 1,25 dihydroxy-Vitamin D, which has shown to lead to improvements in bone mineral metabolism and healing of rickets, thereby increasing growth, mobility, and physical functioning.

4.3 There is no clinical data on burosumab treatment for (i) children as they transition to adults (and change from two weekly dosing to four weekly dosing); or (ii) patients who recommence burosumab therapy as adults following treatment as a child. The TGA Delegate's Overview also noted that the clinical trial data in adolescents (aged 13 to 17 years) remain lacking, despite the importance of the pubertal growth spurt. Nevertheless, the TGA indication supported continued use in adolescents when

clinically indicated. It was noted that the FDA also recently approved burosumab for treatment of XLH in paediatrics aged from 6 months.

4.4 If listed on the PBS, it was anticipated that burosumab would replace 100% of conventional therapy in children and adolescents and 40-70% in adults, although no data was available to inform current treatment patterns among prevalent Australian adult XLH patients. The key differences between the current and proposed clinical management algorithms in the resubmission was the inclusion of burosumab as a treatment option for all Australian XLH patients (paediatrics and adults), with burosumab expected to replace conventional therapy in eligible patients.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The resubmission again nominated conventional therapy (oral phosphorus and calcitriol) as the appropriate comparator. The main clinical evidence for the adult population, however, was based on a comparison of burosumab and placebo. The modelled economic evaluation and financial estimates assumed 70.1% of the adult population are treated with conventional therapy. The ESC considered that the nominated comparator was appropriate.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (175), health care professionals (12) and organisations (2) via the Consumer Comments facility on the PBS website. Of the comments from individuals, the PBAC noted several were from individuals living with XLH, or supporting someone with XLH, who had direct experience of using burosumab. The comments described the disabling nature of XLH, the range of benefits of treatment with burosumab for both paediatric and adult patients including the ease of administration compared to currently available therapies, the effectiveness of the treatment, the tolerability of the treatment and the improved quality of life associated with the treatment. Health professionals described the clinical and quality of life improvements in patients receiving burosumab.

6.3 The PBAC noted the advice received from the Australian and New Zealand Bone and Mineral Society (ANZBMS) and the Australasian Paediatric Endocrine Group (APEG) strongly supporting the use of burosumab in clinical practice. The PBAC specifically noted the advice that the use of burosumab may reverse the serious disabilities

associated with XLH and significantly improve quality of life. The PBAC noted that this advice complemented the evidence provided in the submission for paediatric and adult patients.

Clinical studies

6.4 For the paediatric population, the clinical data was based on one head-to-head randomised trial (CL301) comparing burosumab to conventional therapy (oral phosphorus plus calcitriol) and three non-comparative studies (CL201, CL205 and KRN23-003) as supportive evidence. Data was only available for children aged 1 to 12 years.

6.5 For the adult population, the resubmission was based on one randomised trial (CL303) comparing burosumab to placebo and six non-comparative studies (BUR02, CL304, KRN-INT-001, KRN-INT-002, KRN-US-02 and CL203) as supportive evidence. CL303 included a double-blind placebo-controlled period and two open-label treatment extension periods. BUR02 was an extension study which enrolled a subset of patients that completed the initial treatment extension period in CL303. CL304 was a single-arm study evaluating the effect of burosumab on XLH-related osteomalacia in adults who have not received conventional therapy in the past 2 years. As KRN23-US-02, KRN23-INT-001 and KRN23-INT-002 were dose-finding, dose-escalation or dose-extension studies and the burosumab dose regimens used were inconsistent with the TGA approved dose of burosumab 1.0 mg/kg SC Q4W their results are not presented below. In CL203, although a subgroup of 10 (50%) patients received the TGA approved dose of burosumab during the study, the ESC noted that the results for this relevant subgroup were not provided in the resubmission.

6.6 Details of the studies presented in the submission are provided in Table 4 below.

Table 4: Studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Paediatric studies		
CL301 NCT02915705	UX023-CL301 Clinical Study Report (End of Study (EOS); up to 124 weeks) A Randomized, Open-Label, Phase 3 Study to Assess the Efficacy and Safety of KRN23 Versus Oral Phosphate and Active Vitamin D Treatment in Pediatric Patients with X-linked Hypophosphatemia (XLH). Imel E, Glorieux FH, Whyte MP, et al. Burosumab versus conventional therapy in children with X-linked hypophosphataemia: a randomised, active-controlled, open-label, phase 3 trial.	16 December 2019 The Lancet 2019; 393(10189):2416-2427
CL201 NCT02163577	UX023-CL201 Clinical Study Report (EOS, Week 160): A Randomized, Open-Label, Dose Finding, Phase 2 Study to Assess the Pharmacodynamics and Safety of the anti-FGF23 Antibody, KRN23, in Pediatric Patients with X-linked Hypophosphatemia (XLH). Carpenter T, Whyte M, Imel E, et al. Burosumab Therapy in Children with X-Linked Hypophosphatemia.	5 April 2019 New England Journal of Medicine 2018; 378(21):1987-1998

Trial ID	Protocol title/ Publication title	Publication citation
CL205 NCT02750618	UX023-CL205 Clinical Study Report (Week 64, EOS): An Open-Label, Phase 2 Study to Assess the Safety, Pharmacodynamics, and Efficacy of KRN23 in Children from 1 to 4 Years Old with X-linked Hypophosphatemia (XLH). Whyte M, Carpenter T, Gottesman G, et al. Efficacy and safety of burosumab in children aged 1–4 years with X-linked hypophosphataemia: a multicentre, open-label, phase 2 trial.	24 January 2020 The Lancet Diabetes & Endocrinology 2019; 7(3):189-199.
KRN23-003 NCT03233126	KRN23-003 EOS CSR. A Phase 3 Open-Label Trial to Assess the Efficacy and Safety of KRN23 in Pediatric Patients with X-linked Hypophosphatemic Rickets/Osteomalacia and a Post-marketing Study of KRN23 Switched from the Phase 3 Trial	24 September 2020.
Adult studies		
CL303 NCT02526160	UX023-CL303 EOS, Week 96 CSR. A Randomised, Double-Blind, Placebo-Controlled, Phase 3 Study with Open-Label Extension to Assess the Efficacy and Safety of KRN23 in Adults with X-linked Hypophosphatemia (XLH). Insogna KL, Briot K, Imel EA, et al. A Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial Evaluating the Efficacy of Burosumab, an Anti-FGF23 Antibody, in Adults With X-Linked Hypophosphatemia: Week 24 Primary Analysis.	19 September 2019 Journal of Bone and Mineral Research 2018; 33(8):1383-1393.
BUR02 NCT03920072	BUR02 CSR. A Pre-specified Analysis of the Maintenance of Effect of Burosumab Treatment Across all Time Points Collected from the 96-week Phase 3 UX023-CL303 Study through to Week 48 of the Phase 3b BUR02 Study in 31 Adults with X-linked Hypophosphataemia (XLH).	30 April 2021
CL304 NCT02537431	UX023-CL304 EOS, Week 96. An Open-Label, Single-Arm, Phase 3 Study to Evaluate the Effects of KRN23 on Osteomalacia in Adults with X-linked Hypophosphatemia (XLH). Insogna KL, Rauch F, Kamenický P, et al. Burosumab improved histomorphometric measures of osteomalacia in adults with X-linked hypophosphatemia: a phase 3, single-arm, international trial.	13 November 2019 Journal of Bone and Mineral Research 2019; 34(12):2183-2191.
KRN23-US-02 NCT00830674	KRN23-US-02 Final CSR (single dose). A Phase I, Double-blind, Randomised, Placebo-controlled, Single-dose, Dose-escalation Study of KRN23 in X-linked Hypophosphatemia Patients. Carpenter TO, Imel EA, Ruppe MD, et al. Randomised trial of the anti-FGF23 antibody KRN23 in X-linked hypophosphatemia.	2 May 2013 Journal of Clinical Investigation 2014; 124 (4):1587-1597.
KRN23-INT-001 NCT01340482	KRN23-INT-001. Final CSR (four doses, 28 day intervals). A Phase 1/2, Open-Label, Repeat-Dose, Dose-Escalation Study of KRN23 in Adult Patients with X-Linked Hypophosphatemia. Imel EA, Zhang X, Ruppe MD, et al. Prolonged Correction of Serum Phosphorus in Adults with XLH Using Monthly Doses of KRN23.	13 May 2014 The Journal of Clinical Endocrinology & Metabolism 2015; 100(7):2565-73.
KRN23-INT-002 NCT01571596	KRN23-INT-002 Final CSR (extension study of KRN23-INT-001, up to 12 doses, 28 day intervals). An Open-Label, Long-Term, Extension Study to Evaluate the Safety and Efficacy of KRN23 in Adult Patients with X-Linked Hypophosphatemia. Imel EA, Zhang X, Ruppe MD, et al. Prolonged Correction of Serum Phosphorus in Adults with XLH Using Monthly Doses of KRN23.	10 June 2014 The Journal of Clinical Endocrinology & Metabolism 2015; 100(7):2565-73.

Trial ID	Protocol title/ Publication title	Publication citation
CL203 NCT02312687	UX023-CL203 EOS, Week 72 CSR. A Phase 2b, Open-Label, Long-Term Extension Study To Evaluate The Safety And Pharmacodynamics Of KRN23 In Adult Patients With X-Linked Hypophosphatemia (XLH). Ruppe M, Peacock M, Weber T, et al. Clinical and Radiographic Characteristics of Adult XLH in a Cohort of Patients Treated with KRN23, an Antibody to FGF23 [Abstract]	20 November 2019 ASBMR September 16-19, 2016, Atlanta

Blue shading indicates data previously seen by the PBAC.
Source: Tables 2-2 and 2.3, pp41-42 of the resubmission.

Paediatrics

6.7 The key features of the included paediatric trials are summarised in Table 5.

Table 5: Key features of the included evidence for paediatrics

Trial	N	Design/ duration	Bias	Treatment arms	Population	Outcome(s)	Modelled evaluation
BUR vs conventional therapy (oral phosphorus plus calcitriol)							
CL301	61	R, MC, OL 64 wks (OL extension, results up to 88 wks[e])	Low-Moderate	BUR 0.8 mg/kg Q2W[a] Conventional therapy[b]	Age 1-12; XLH	1°: RGI-C (Wk 40) 2°: RSS, growth Other: 6MWT, PD, QoL, AEs	RSS
Supportive studies							
CL201	52	R, MC, OL, parallel 64 wks (OL extension, results up to 160 wks for efficacy & 214 wks for safety)	Low-Moderate	BUR 0.1/0.2/0.3 mg/kg Q2W[c] BUR 0.2/0.4/0.6 mg/kg Q4W[c]	Age 5-12; XLH	1°: RSS (Wk 40) 2°: RGI-C, growth, 6MWT Other: PD, QoL, AEs	RSS
CL205	13	MC, OL 64 wks (OL extension, results up to 160 wks)	Low-Moderate	BUR 0.8 mg/kg Q2W[d]	Age 1-4; XLH	1°: serum phosphorus (Wk 40) 2°: RGI-C, RSS Other: PD, AEs	RSS
KRN23-003	15	MC, OL 40 wks (OL extension, results up to 124 wks)	Low-moderate	BUR 0.8 mg/kg Q2W (self-administered)[f]	Age 1-12 XLH	1°: AEs 2°: RSS, RGI-C, 6MWT, growth	Not used

Blue shading indicates data previously seen by the PBAC.
Source: Sections 2.3.1.1 to 2.3.1.4, pp46-49 of the resubmission.

AEs=adverse events; BUR=burosumab; DB=double blind; MC=multi-centre; OL=open label; PD=pharmacodynamic; R=randomised; RGI- C=Radiographic Global Impression of Change; RSS=Rickets Severity Score; XLH=X-linked hypophosphataemia; 6MWT=Six-minute Walk Test; Q2W=every 2 weeks; Q4W=every 4 weeks; wk(s)=week(s);

a BUR initiated at 0·8 mg/kg Q2W injected subcutaneously by a health-care professional at the study site or during a home health visit, and increased to 1·2 mg/kg Q2W if two consecutive pre-dose fasting serum phosphorus concentrations were <1.03 mmol/L (3.2 mg/dL) and serum phosphorus increased by <0.16 mmol/L (0·5 mg/dL) from baseline on a single measurement.

b Oral phosphate dose is 20-60 mg/kg per day divided into three to five doses per day, and alfacalcidol 40-60 ng/kg per day or calcitriol 20-30 ng/kg per day. Depending on the formulation, the active vitamin D could be given one to three times a day.

c Patients were enrolled sequentially into cohorts defined by the initial dose of BUR. Within each cohort, patients were randomized to Q2W or Q4W regimen i.e. Dose Cohort 1 received initial doses of 0.1 mg/kg Q2W or 0.2 mg/kg Q4W, Dose Cohort 2 received initial doses of 0.2 mg/kg Q2W or 0.4 mg/kg Q4W; Dose Cohort 3 received initial doses of 0.3 mg/kg Q2W or 0.6 mg/kg Q4W. During the titration period (16 week), dose was adjusted every 4 weeks in 0.3mg/kg increments to meet serum phosphorus targets.

d BUR initiated at 0·8 mg/kg Q2W and dose was increased to 1.2 mg/kg at any time during the study when a patient met all the dose-adjustment criteria: 2 consecutive serum phosphorus measurements below the normal range; serum phosphorus increased by <0.5 mg/dL from Baseline; and the patient had not missed a dose of study drug that would have accounted for the decrease in serum phosphorus.

e the resubmission reported (p46) that data are now available to a maximum of 124 weeks of treatment and follow up, however results up to only 88 weeks are presented in the submission.

f BUR starting dose was 0.8 mg/kg SC Q2W, which could be increased to 1.2 mg/kg at any time during the study if a subject met specified dose-adjustment criteria. Self-administration (by patient/carer) was permitted from Week 4.

6.8 Details of CL301, CL201 and CL205 were unchanged from the March 2021 submission. In KRN23-003, patients were permitted to self-administer (by patient/carer) burosumab treatment from Week 4. Treatment duration was 40 weeks but patients could continue treatment in the extended treatment period (up to Week 124).

Adults

6.9 The key features of the included adult trials are summarised in Table 6.

Table 6: Key features of the included evidence for adults

Trial	N	Design/ duration	Bias	Treatment arms	Population	Outcomes	Modelled evaluation
BUR vs placebo							
CL303	134	R, MC, DB, PC 24 wks (OL extension ≤125 wks)[a]	Low-moderate	BUR 1 mg/kg SC Q4W PBO SC Q4W	Age 18-65; XLH	1°: serum phosphorus[b] (Wk 24) 2°: BPI, WOMAC Other: PD, fractures, 6MWT, TUG	WOMAC, fractures
Supportive studies							
BUR02	31[c]	OL extension 48 wks	High	BUR 1 mg/kg SC Q4W	Age 18-65; XLH	Serum phosphorus[d], PRO (WOMAC, BPI), 6MWT, TUG	Not used
CL304	14	MC, OL 48 wks (OL extension, results up to 96 wks)[e]	High	BUR 1 mg/kg SC Q4W	Age 18-65; XLH, no CT past 2y	1°: OV/BV (48 wks) 2°: serum phosphorus, fractures	Not used
KRN23-US-02	38	R, DB, PC 15 days[f] f/up, results up to 50 days	High	BUR 0.1-1 mg SC BUR 0.003-0.3 mg/kg IV PBO SC or IV[g]	Age ≥18, XLH	1°: safety (AEs) 2°: PD (incl serum phosphorus)	Not used
KRN23-INT-001	28[h]	MC, OL 120 days	High	BUR 0.05-0.6 mg/kg SC[i]	Age ≥18, XLH	1°: serum phosphorus 2°: PD, WOMAC	Not used
KRN23-INT-002	22[j]	MC, OL 13.5 months	High	BUR[k] 0.05, 0.1, 0.3, 0.6, or 1.0 mg/kg SC Q4W	Age ≥18, XLH	1°: serum phosphorus 2°: PD, WOMAC	Not used
CL203	20[l]	OL extension, results up to 168 wks	High	BUR[m] 0.3, 0.6, or 1.0 mg/kg SC Q4W	Age ≥18, XLH	1°: safety, PD Other: fractures, WOMAC, BPI	Not used

Source: compiled during the evaluation based on information presented in Sections 2.3.2 to 2.3.2.6, pp50-55 of the resubmission.

1°=primary, 2°=secondary, AEs=adverse events; BPI=Brief Pain Inventory; BUR=burosumab; CT=conventional therapy; DB=double blind; MC=multi-centre; OL=open label; OV/BV=osteoid volume (OV)/ bone volume (BV); PD=pharmacodynamic; PRO=patient reported outcomes; R=randomised; TUG=timed up and go; WOMAC=Western Ontario & McMaster University Osteoarthritis Index; XLH=X-linked hypophosphataemia; 6MWT=Six-minute Walk Test; Q2W=every 2 weeks; Q4W=every 4 weeks; wk(s)=week(s);

a Following placebo-controlled treatment (24 weeks), patients entered OL treatment continuation in which all patients received BUR (Wks 24-48) followed by OL treatment extension period I (Weeks 48–96), and OL treatment extension period II (to Wk 149 for some patients in US and EU). The study has completed; however, results are available to end of treatment extension period I (Wk 96) only due to operational issues.

b Primary outcome was the proportion of patients with mean serum phosphorus above the LLN (2.5 mg/dL [0.81 mmol/L]) at the midpoint of the dose interval (i.e., Wks 2, 6, 10, 14, 18, and 22), as averaged across dose cycles between Baseline and Wk 24.

c All patients were previously enrolled in CL303. However, not all patients enrolled into BUR02 continued BUR treatment after the final study visit of CL303 before enrolling into BUR02.

d In BUR02 only trough serum phosphate samples measured (secondary outcome in CL303). The samples from the two studies were analysed by different central laboratories, with slightly different LLN (0.81 mmol/L in CL303; 0.74 mmol/L in BUR02).

e CL304 comprised 3 treatment periods: OL treatment period, treatment extension I, and treatment extension II. Subjects who completed 48-wk OL treatment period continued into 48-wk treatment extension I (to Wk 96). For subjects at study sites outside US, Wk 96 was the End of Study I (i.e. EOS I) and subjects (n=8) at sites in the US, treatment continued up to an additional 45 wks (i.e. EOS II).
f Patients were administered a single-dose of study drug on Day 1 and confined to the Clinical Research Unit for 6 nights (Day -2 to Day 5) and returned for non-confined Observation Period (Days 1 to 15) for evaluation and follow-up (Day 16 to 50).
g Each BUR treatment arms (IV and SC) had 4 patients randomized 3:1 to receive a single-dose of BUR or placebo. There were 5 dose levels (Cohorts 1-5) in BUR IV arm (0.003, 0.01, 0.03, 0.1, and 0.3 mg/kg) and 4 dose levels (Cohorts 4-7) in BUR SC arm (0.1, 0.3, 0.6 and 1.0 mg/kg). Dose-escalation was based on safety (AEs) and efficacy (serum phosphorus) once all patients in the prior cohort completed the observation period (Day 15).
h 28 subjects were treated with BUR; 27 in the OL phase and 1 in the bone sub study (randomised single-blind extension study of BUR vs placebo on bone parameters) which was subsequently terminated due to slow accrual after n=2 subjects were randomised.
i Each subject received 4 doses of BUR (1 every 28 days) in stepwise dose-escalation (0.05-> 0.1-> 0.3-> 0.6 mg/kg SC) over 120 days.
j KRN23-INT-002 was a long-term extension study that enrolled subjects who previously completed the OL phase of KRN23-INT-001.
k Initial BUR dose was selected based on the subject's serum phosphorus levels on Day 84 (Visits 20) in KRN-INT-001.
l CL203 enrolled patients who had participated in KRN23-INT-001 or KRN23-INT-002 (received at least 2 doses of BUR).
m Starting BUR doses matched the last dose in KRN23-INT-001 or KRN23-INT-002 and based on subjects' body weight at Day 0.

6.10 CL303 was a multicentre, double-blind, randomised trial comparing burosumab with placebo in adult patients with XLH using TGA approved doses for a duration of 24 weeks, followed by open-label extension where all patients received burosumab up to Week 96 (and Week 149 for some patients in the US and EU). The primary outcome was proportion of patients with mean serum phosphorus above the lower limit of normal (LLN) as averaged across dose cycles between baseline and Week 24. For a subset of patients who had previously enrolled in CL303, treatment with open-label BUR was maintained for an additional 48 weeks in the BUR02 extension study. CL303 was conducted in parallel with CL304.

6.11 In CL303 and CL304, patients initiated burosumab 1.0 mg/kg SC Q4W (28 days) based on baseline weight (rounded to the nearest 10 mg) up to a maximum dose of 90 mg. The dosing strategy was based on the three burosumab early phase studies (KRN23-US-02, KRN23-INT-001 and KRN23-INT-002), which found that after the initial dose-titration period, most patients stabilised on an optimal dose of burosumab 1.0 mg/kg and achieved serum phosphorus levels within the normal range. The safety data indicated that repeated monthly doses up to 1.0 mg/kg were well tolerated by adult patients with XLH.

6.12 Baseline characteristics were generally balanced between treatment groups in CL303, but there were some differences in terms of medical history with more patients in the burosumab group with a history of osteoarthritis, renal conditions and dental/oral conditions compared to placebo. Across the studies, there were some differences in the baseline characteristics in terms of the proportion of patients with positive PHEX mutation (higher in CL304), proportion who initiated conventional therapy before age 18 (lower in CL203), active pseudofractures (lower in CL304) and serum phosphorus (higher in BUR02 and CL304).

6.13 The overall risk of bias for the included adult studies (apart from CL303 which was a randomised double blind RCT) was considered high mainly due to the studies being open-label and non-randomised. Therefore, patients were aware of their treatment allocations. While the efficacy outcomes in terms of pharmacodynamic (PD)

parameters (serum phosphorus) or osteoid volume were objective measurements, other patient outcomes such as Western Ontario & McMaster University Osteoarthritis Index (WOMAC) or Brief Pain Inventory (BPI) and adverse events (AEs) were subjective outcomes and may be affected by reporting bias, particularly for within-group comparisons to baseline.

Comparative effectiveness

6.14 All the included (paediatric and adult) studies measured serum phosphate/PD biochemical outcomes as primary and secondary outcomes. For the paediatric studies, all patients were enrolled with PHEX mutation or FGF23 level and biochemical findings (including serum phosphorus level and serum 25(OH)D), and radiographic evidence with rickets severity score (RSS). For the adult studies, patients were enrolled with clinical features of XLH (e.g. short stature or bowed legs) and PHEX mutation and/or FGF23 level and biochemical findings that included serum phosphorus and TmP/GFR.

Paediatrics

6.15 At the March 2021 meeting, the PBAC noted that "the primary outcomes presented, and used to quantify the clinical effectiveness of burosumab in children, were the rickets severity score (RSS) and the radiographic global impression of change (RGI-C) and that these outcomes did not capture aspects of XLH which were important to patients such as changes in gross motor skills, the need for corrective surgery, pain and oral health." (paragraph 7.6, burosumab Public Summary Document [PSD], March 2021). The outcomes presented in the resubmission for the clinical effectiveness of burosumab in paediatrics remain unchanged. The Pre-Sub-Committee Response (PSCR) acknowledged that the outcomes presented were a limitation of the available clinical data, stating that irrespective of whether the RSS response criterion (defined as ≥ 1 point change from baseline) was appropriate, the differences between groups observed were not driven by the response definition, but by the comparative effectiveness of the respective therapies.

6.16 Table 7 summarises the change from baseline in PD parameters (serum phosphorus) at Week 40 and Week 64 in the paediatric studies.

Table 7: Change from baseline in PD parameters (serum phosphorus) at Week 40 and Week 64 in the paediatric studies (ITT)

Outcome	CL301		CL201	CL205	KRN23-003
	BUR Q2W N=29	Conventional N=32	BUR Q2W[a] N=26	BUR Q2W N=13	BURQ2W[# a] N=15
PD markers					
Serum phosphate (mg/dL)					
Baseline, mean (SD)	2.42 (0.24)	2.30 (0.26)	2.38 (0.41)	2.51 (0.28)	2.61 (0.32)
Week 40, mean (SD)	3.38 (0.37)	2.55 (0.29)	3.30 (0.40)	3.47 (0.49)	3.51 (0.45)
Week 40, LS mean (SE) change from baseline	+1.00 (0.062)	+0.23 (0.058)	+0.92 (0.094)	+0.96 (0.12)	+0.90 (0.30)
Difference (95%CI) v conventional	**0.77 (0.60, 0.94)**		-	-	-
Week 64, mean (SD)	3.36 (0.37)	2.56 (0.30)	3.35 (0.45)	3.40 (0.48)	3.49 (0.46)
Week 64, LS mean (SE) change from baseline	+0.98 (0.061)	+0.24 (0.058)	+0.99 (0.10)	+0.89 (0.11)	+0.88 (0.31)
Difference (95%CI) v conventional	**0.74 (0.58, 0.91)**		-	-	-
n (%) reach normal range (3.2-6.1 mg/dL)					
Baseline to end of treatment period[b]	28 (96.6)	24 (75.0)	24 (92.3)	13 (100)	-
Week 40	18 (62.1)	1 (3.1)	17 (65.4)	10 (76.9)	5 (33.3)
Week 64	19 (65.5)	1 (3.1)	16 (66.7)	8 (61.5)	6 (40.0)

Blue shading indicates data previously seen by the PBAC.

Source: Section 2.5.1.1.2.1, pp118-119 of the resubmission, Table 14.2.3.1.1.1.1, pp1410-1446 of CL301_EOS_report-body, Table 14.2.3.1.1, pp2190-2269 of CL201_EOS_report-body, Table 14.2.3.1.1, pp576-614 of CL205_EOS_report-body, Table 14.2.1-1.1, pp139-154, Table 14.3.5-2, pp801-803 of KRN23-03 CSR.

BUR=burosumab; ITT=intention-to-treat; LS=least squares; PD=pharmacodynamic; Q2W=every 2 weeks

Self-administration (by patient/carer) was permitted from Week 4.

a Mean (SE) change from baseline not reported as LS mean (SE) change from baseline.

b Proportion of patients that had a serum phosphorus concentration within the normal range (3.2 to 6.1 mg/dL [1.03 to 1.97 mmol/L]) at least once during the treatment period.

6.17 In CL301, a higher proportion of patients in the burosumab group achieved serum phosphorus within the normal range (3.2-6.1 mg/dL) at least once during the treatment period. The proportion of patients with serum phosphorus level within the normal range at Week 40 and Week 64 were consistent across the studies (except in KRN23-003 which had a lower proportion of patients achieving normal serum phosphorus levels).

Adults

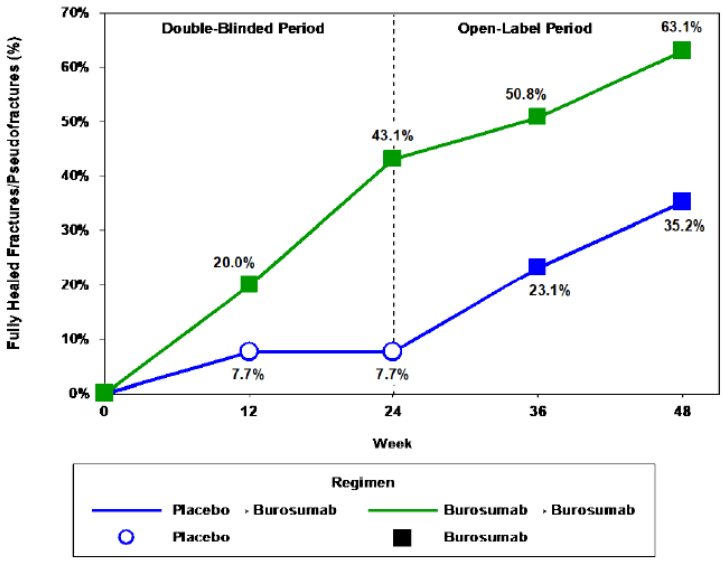
6.18 The resubmission stated that in adults with XLH, burosumab was given to directly treat the underlying pathophysiology of the FGF23-induced hypophosphatemia and improve phosphate homeostasis, skeletal health (i.e. fracture healing), patient reported outcomes including stiffness and pain, and mobility. The resubmission nominated the relevant outcomes as: i) fracture healing, ii) biochemical markers of phosphate homeostasis and bone mineralisation (serum phosphate, serum 1,25(OH)2D and TmP/GFR), iii) markers of bone formation and resorption (procollagen type 1 N-propeptide (P1NP) and carboxy-terminal cross-linked telopeptide of type I collagen (CTx) and bone-specific alkaline phosphatase (BALP), iv) patient reported outcome of stiffness, pain and fatigue (WOMAC, BPI and brief fatigue index (BFI)) and iv) physical function (6MWT and timed up and go (TUG)).

6.19 The nominated outcomes were generally consistent with the recommended clinical, biochemical and radiological follow-up assessment of adults with XLH based on guidance for the diagnosis and management of XLH (Haffner et al 2019) [6]. However, only the outcomes of fractures healing and WOMAC (stiffness, pain and fatigue) from CL303/BUR02 were used in the modelled economic evaluation for adults with XLH.

6.20 The resubmission did not clearly specify a minimally clinically important difference (MCID) for WOMAC. There were small inconsistencies in the meaningful change threshold presented in the resubmission, which was based on the responder definitions for XLH from Skrinar et al 2019. Skrinar et al 2019 defined response as 10-15 point decrease for the stiffness domain, 8-10 point decrease for the physical function domain, 11 point decrease for the pain domain and 10 points for the total score.

6.21 Figure 1 illustrates the percentage of healed active fractures and pseudofractures over time in CL303. At baseline 32 patients (47.1%) in burosumab group had a combined total of 65 active fractures (14 fractures and 51 pseudofractures), and 38 (57.6%) patients in the placebo group had 91 active fractures (13 fractures and 78 pseudofractures).

Figure 1: Percentage of healed active fractures and pseudofractures in CL303



Source: Figure 2-43, p161 of the resubmission.

6.22 The results demonstrated that:

[6] Haffner D, Emma F, Eastwood DM, et al. 2019. Clinical practice recommendations for the diagnosis and management of X- linked hypophosphataemia: Consensus Statement. Nature Reviews Nephrology 15(7):435-455.

- during the placebo-controlled treatment period, the percentage of baseline active fractures/pseudofractures graded as fully healed at Week 24 was higher in the burosumab group compared to placebo (43.1% v 7.7%). After placebo crossover to burosumab treatment in the open-label treatment continuation period, 63.1% (41/65) fractures in the burosumab group had fully healed compared to 35.2% (32/91) fractures in the placebo-burosumab crossover group at Week 48.
- the number of patients with active fractures/pseudofractures graded as fully healed in the burosumab groups increased from baseline at Week 24 (50%) and Week 48 (65.6-75%). The number patients with active fractures/pseudofractures graded as fully healed for the burosumab groups were consistent between CL303 and CL304.

Fracture healing was an exploratory outcome across the studies and reported up to Week 48. However, the CL303 CSR (p181) stated that beyond Week 48, x-ray follow-up was continued only on 'new findings' of fractures/pseudofractures identified at Weeks 12 to 48, of which 56% (10/18) were fully healed or partially healed at the end of study I (i.e. last time point imaged on study, Week 96).

6.23 Table 8 summarises the change from baseline in the PD parameters (serum phosphorus) in the adult studies.

Table 8: change from baseline in PD (serum phosphorus) in the adult studies

Outcome	CL303		BUR02 [a]	CL304
	BUR Q4W N=68	Placebo N=66	BUR Q4W N=31	BUR Q4W N=14
Serum phosphate (mg/dL)^#				
Baseline, mean (SD)	2.03 (0.30)	1.92 (0.32)	2.26 (0.12)[b]	2.24 (0.40)
Week 24, mean (SD)	2.53 (0.45)	2.07 (0.34)	2.45 (0.077)[b]	2.60 (0.33)
Week 24, LS mean (SE) change from baseline	0.39 (0.081)	-0.01 (0.067)	0.53 (0.062)[c]	0.35 (0.073)
Difference (p-value) vs placebo	**p<0.0001**		-	-
n (%) >LLN Week 0-24 across midpoints of dose cycles	63 (92.6)[d]	5 (7.6)[d]	-	13 (92.9)
n (%) >LLN Week 0-24, across ends of dose cycles	46 (67.6)	4 (6.1)	-	11 (78.6)
Week 48, mean (SD)	2.48 (0.46)	2.47 (0.49)	2.45 (0.074)[b]	2.43 (0.30)
Week 48, LS mean (SE) change from baseline	0.34 (0.077)	0.39 (0.078)	0.53 (0.068)[c]	0.17 (0.079)
n (%) >LLN Week 24-48 across midpoints of dose cycles	57 (83.8)	59 (89.4)	-	-
Week 96, mean (SD)	2.52 (0.42)	2.32 (0.48)	-	2.47 (0.32)
Week 96, LS mean (SE) change from baseline	0.38 (0.074)	0.24 (0.077)	-	0.20 (0.089)
n (%) >LLN Week 48-96 across midpoints of does cycles	56 (82.4)	45 (68.2)	-	-

Source: Tables 2-67 to 2-68, pp154-155, Table 2-74, p169, Table 2-81, p189- of the resubmission.

BUR=burosumab; LLN=lower limit of normal; LS=least squares; PD=pharmacodynamic; Q4W=every 4 weeks;

^ serum phosphate LLN was 2.5 mg/dL (0.81 mmol/L) in CL303, CL304, and 2.3 mg/dL (0.74 mmol/L) in BUR02.

serum phosphorus was assessed at the midpoints (i.e. 2 weeks after each dose of study drug; time of peak PD effect) of the dose cycles and the ends (i.e. 4 weeks after dosing; time of trough PD effect of the dose cycles) in CL303 and CL304. In BUR02, only trough serum phosphate samples were measured.

‡ end of dose interval and time of trough PD effect.

a Phosphate values reported as mmol/L; 1 mg/dL=0.323 mmol/L.

b mean (SE) trough serum phosphate level
c LS mean change from CL303 baseline trough serum phosphate level 1.95 mg/dL [0.63 mmol/L]
d Primary endpoint in CL303 was the proportion of patients achieving mean serum phosphorus above LLN at the midpoint of the dose interval (i.e. Weeks 2, 6, 10, 14, 18, and 22), as averaged across dose cycles between baseline and Week 24.

6.24 The results demonstrated that:

- all post-baseline mean levels of serum PD biochemical and bone biomarkers remain above the baseline levels over the duration of the studies in all treatment groups. The mean change from baseline in serum PD biochemical markers at Week 24 for the burosumab group were broadly consistent between CL303 and CL304. Results after Week 24 were varied possibly due to heterogeneity between the studies.
- in CL303, during the placebo-controlled treatment period, the mean change from baseline in serum phosphorus, serum 1,25(OH)2D phosphate reabsorption (TmP/GFR), and bone biomarkers (P1NP and CTx) at Week 24 were statistically significantly greater in the burosumab group compared to placebo.
- the proportion of patients that achieved mean serum phosphorus above LLN across the midpoints (and ends) of the dose intervals from baseline to Week 24 was higher in the burosumab group compared to the placebo group. For CL303, pre-specified sensitivity analyses adjusting for the actual randomisation stratification by BPI (Question 5) Average Pain rather than the planned stratification by BPI (Question 3) Worst Pain showed similar results to the primary analysis.

6.25 Noting that there was no direct evidence comparing burosumab against the nominated comparator (i.e. conventional therapy), the PSCR stated that post hoc analyses of screening visit data from the CL303 trial indicated that there was virtually no difference in the proportion of patients with serum phosphate ≥ LLN between patients receiving or not receiving phosphorus supplements at the time of study entry. The PSCR suggested that the effectiveness of conventional therapy on serum phosphate levels in an adult population with established, symptomatic XLH, was probably not different to placebo.

6.26 Table 9 summarises the patient reported outcomes for WOMAC from the included adult studies.

Table 9: Patient reported outcomes (WOMAC) in the adult studies

Outcome	CL303^		BUR02
	BUR Q4W N=68	Placebo N=66	BUR Q4W N=31
WOMAC physical function			
Baseline, mean (SD)	50.79 (19.66)	43.89 (19.94)	43.75 (3.23)[a]
Week 24, mean (SD)	43.43 (19.51)	42.65 (22.76)	38.50 (3.35)[a]
Week 24, LS mean (SE) change from baseline	-3.11 (2.55)	+1.79 (2.72)	−15.84 (2.69)[b]
Difference (SE) vs placebo	-4.90 (2.48)		-
Week 48, mean (SD)	38.35 (18.61)	34.74 (22.62)	35.86 (3.29)[a]
Week 48, LS mean (SE) change from baseline	-8.42 (2.06)	-7.15 (2.80)	−18.03 (2.69)[b]
Week 96, mean (SD)	38.51 (20.62)	34.02 (22.70)	-
Week 96, LS mean (SE) change from baseline	-9.02 (2.27)	-8.41 (2.75)	-
WOMAC Stiffness			
Baseline, mean (SD)	64.71 (20.25)	61.36 (20.77)	53.33 (3.49)[a]
Week 24, mean (SD)	53.73 (20.76)	60.38 (21.83)	45.56 (3.87)[a]
Week 24, LS mean (SE) change from baseline	-7.85 (3.03)	+0.46 (3.14)	−19.93 (3.92)[b]
Difference (SE) vs placebo	**-8.31 (3.25)**		
Week 48, mean (SD)	45.27 (21.90)	44.70 (22.47)	43.75 (3.37)[a]
Week 48, LS mean (SE) change from baseline	-16.63 (3.30)	-15.83 (3.49)	−22.93 (3.54)[b]
Week 96, mean (SD)	47.25 (24.79)	42.58 (24.02)	-
Week 96, LS mean (SE) change from baseline	-15.32 (3.58)	-17.67 (3.74)	-
WOMAC Stiffness response (reduction in WOMAC stiffness score ≥ 10.0)			
Week 24, n (%)	40 (59)	30 (45.5)	-
Week 48, n (%)	46 (68.2)	45 (68.2)	-
Week 96, n (%)	38 (64.4)	40 (67.8)	-
WOMAC pain			
Baseline, mean (SD)	50.67 (18.01)	47.95 (15.54)	41.00 (2.65)[a]
Week 24, mean (SD)	43.36 (17.11)	45.23 (18.38)	35.00 (3.24)[a]
Week 24, LS mean (SE) change from baseline	-	-	−14.38 (3.09)[b]
Week 48, mean (SD)	37.50 (16.53)	36.21 (20.34)	35.36 (3.0)
Week 48, LS mean (SE) change from baseline	-	-	−13.84 (3.13)
Week 96, mean (SD)	35.59 (17.59)	36.36 (20.80)	-
Week 96, LS mean (SE) change from baseline	-	-	-

Source: Table 2-73, p162 and Table 2-75, p171 of the resubmission, Table 14.2.1.2.3.1.99, pp1885-1929, Table 14.2.1.2.3.1 of CL303 CSR, p1930-1938.

BUR=burosumab; LS=least squares; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index; Q4W=every 4 weeks;

^ LS means and p-values estimated from GEE model, which included the change from baseline for the endpoint of interest as the dependent variable; region, visit, treatment, actual randomization stratification (not included for analysis of BPI Worst Pain), and visit by treatment as fixed factors; and baseline value for the endpoint of interest as a covariate, with compound symmetry covariance structure.

a mean (SE) score.

b LS mean (SE) change from CL303 baseline WOMAC physical function score: 51.94 (2.73), WOMAC stiffness score: 64.11 (2.44) or WOMAC pain score: 48.23 (2.38).

6.27 The results demonstrated that:

- there was improved patient reported outcomes in terms of WOMAC (pain, stiffness and physical functioning) domains and BPI (worst pain and pain severity) at Weeks 24 to the end of study (Week 149 in CL303 and Week 48 in BUR02) in all treatment groups compared to baseline.

- in CL303, during the placebo-controlled treatment period, the mean change from baseline in WOMAC stiffness at Week 24 was statistically significantly greater in the burosumab group compared to placebo. The mean difference in WOMAC stiffness at Week 24 potentially may not be clinically meaningful given the point estimate was below the estimated MCID for WOMAC stiffness of 10 points. The PSCR noted that the randomised phase of the study (24 weeks) was insufficient to detect the full impact of burosumab on WOMAC scores.
- the proportion of WOMAC responders (physical function and stiffness) and BPI responders (worst pain) at Week 24 in the burosumab group was numerically higher than in placebo. After placebo crossover to burosumab treatment in the open-label treatment continuation period to Week 96, the proportion of responders were comparable in both treatment groups.

6.28 The resubmission presented the results of mobility outcomes (6MWT and TUG) from CL303 and BUR02. In CL303, there were increases from baseline in 6MWT distance walked with a statistically significant difference between treatment groups at Week 24. The improvement in 6MWT distance walked was generally maintained during the open-label treatment continuation period in CL303 and through study extension in BUR02. In CL303, the TUG outcome was added as a protocol amendment and first administered at Week 36. The results showed TUG time was generally maintained to the end of the study (Week 96 for CL303 and Week 48 for BUR02).

6.29 The resubmission presented a summary of observational studies with conventional therapy and other treatments for XLH in paediatrics and adults. There were no studies evaluating the optimal dose for conventional therapy. For adults, Sullivan et al 1992 reported a small observational study (n=16) in symptomatic patients with XLH followed up for 4.2 years and showed that after treatment with conventional therapy there were statistically significant improvement in bone or joint pain and serum phosphate compared to before therapy. Conventional therapy also decreased but not normalise osteomalacia-related parameters (osteoid thickness and volume). Connor et al 2015 showed in a cross-sectional study (n=52) that conventional therapy in adults with XLH was not associated with the number of sites of enthesopathy and there was no improvement in calcifications of tendons and ligaments, however extended use of conventional therapy for a greater proportion of adulthood was associated with a reduced risk of severe dental disease.

Comparative harms

Paediatrics

6.30 In CL301, a higher proportion of patients treated with burosumab compared to conventional therapy experienced any AEs, treatment-related AEs and injection site reactions. Across the treatment arms, the incidence of serious AEs was low, most AEs were of mild intensity, no patient experienced AEs leading to discontinuation and no

deaths were reported. In KRN23-003, after the start of self-administration of burosumab (at Week 4) all patients experienced TEAEs. The proportion of patients experiencing AEs in the burosumab group were generally similar across the studies.

Adults

6.31 In CL303, during the placebo-controlled treatment period the incidence of any AEs, serious AEs and treatment-related AEs were similar between burosumab and placebo groups. The total incidence of AEs to the end of the study (including the open label treatment continuation period) was higher in the burosumab group compared to placebo-burosumab crossover group, however the exposure-adjusted rate of AEs were similar between the treatment groups.

6.32 The most commonly reported AEs for the burosumab group included nasopharyngitis, back pain, headache and tooth abscess, and for the placebo group included arthralgia, pain in extremity and oropharyngeal pain. Pre-defined AEs of special interest included injection site reactions, hypersensitivity and restless leg syndrome, which were similar between groups, however noting injection site reactions for the placebo group was a result of sham injections for blinding of treatment assignment and would not be observed normally.

Benefits/harms

6.33 A summary of the comparative benefits and harms for burosumab versus conventional therapy in paediatric patients is presented in Table 10 below. All clinically relevant results are summarised; however, the modelled economic evaluation was based solely on RSS results at Week 64 in paediatrics.

Table 10: Summary of comparative benefits and harms for BUR Q2W and conventional therapy in paediatrics

Benefits							
LS mean change from baseline							
CL301^	**Burosumab**			**Conventional**			**Mean difference (95% CI)**
	N	**Mean Δ baseline**	**SE**	**N**	**Mean Δ baseline**	**SE**	
RGI-C, Wk 40^	29	+1.92	0.11	32	+0.77	0.11	**1.14 (0.83, 1.45)**
RGI-C, Wk 64	29	+2.06	0.072	32	+1.03	0.14	**1.02 (0.72, 1.33)**
RSS, Wk 40	29	-2.04	0.15	32	-0.71	0.14	**-1.34 (-1.74, -0.94)**
RSS, Wk 64	29	-2.23	0.12	32	-1.01	0.15	**-1.21 (-1.59, -0.83)**
Standing height/ recumbent length Z Score, Wk 64	29	+0.17	0.066	32	+0.02	0.035	**+0.14 (+0.00, +0.29)**
Growth velocity of standing height/ recumbent length (Z Score), Wk 64	29	+1.53	0.26	32	+0.41	0.27	**+1.12 (0.37, 1.88)**
6MWT (m), Wk 64	29	+75	13	32	+29	17	**+46 (2, 89)**
Serum phosphate (mg/dL), Wk 64	29	+0.98	0.061	32	+0.24	0.058	**0.74 (0.58, 0.91)**
1,25(OH)2D (pg/mL), Wk 64	29	9.89	2.24	32	1.19	2.79	**8.70 (1.72, 15.68)**
TmP/GFR (mg/dL), Wk 64	29	1.16	0.13	32	-0.09	0.07	**1.25 (0.96, 1.54)**
ALP (U/L), Wk 64	29	-174.62	13.43	32	-28.06	19.98	**-146.56 (-191.61, 101.52)**

Harms (Wk 64)						
CL301	**Burosumab n/N**	**Conventional n/N**	**RR (95% CI)**	**Event rate/100 patients***		**RD (95% CI)**
				Burosumab	**Conventional**	
Any AEs	29/29	27/32	**1.18 (1.01, 1.38)**	100	84.4	**0.16 (0.02, 0.29)**
Treatment related AEs	17/29	8/32	**2.34 (1.20, 4.60)**	58.6	25.0	**0.34 (0.10, 0.57)**
General disorders and administration site conditions	25/29	9/32	**3.07 (1.73, 5.43)**	86.2	28.1	**0.58 (0.38, 0.78)**
Gastrointestinal disorders	23/29	17/32	**1.49 (1.03, 2.17)**	79.3	53.1	**0.26 (0.03, 0.49)**
Respiratory, thoracic and mediastinal disorders	21/29	9/32	**2.57 (1.42, 4.68)**	72.4	28.1	**0.44 (0.22, 0.67)**
Skin and subcutaneous tissue disorders	11/29	4/32	**3.03 (1.09, 8.48)**	37.9	12.5	**0.25 (0.04, 0.46)**
Injury, poisoning and procedural complications	10/29	2/32	**5.52 (1.32, 23.12)**	34.5	6.3	**0.28 (0.09, 0.47)**
Predefined injection site reaction TEAEs	15/29	0	**34.10 (2.13, 545.51)**	51.7	0	**0.52 (0.33, 0.70)**

Source: Compiled during the evaluation from Tables 2-46 and 2-51, pp112-116, Tables 2-52 to 2-53, pp123-125, Tables 2-104 to 2-109, pp211-216 of the resubmission.

AE=adverse events; ALP=alkaline phosphatase; LS=least squares; RGI-C=Radiographic Global Impression of Change; RSS=Rickets Severity Score; RD=risk difference; RR=risk ratio; TEAE=treatment emergent adverse event; TmP/GFR=ratio of renal tubular maximum reabsorption rate of phosphate (TmP) to glomerular filtration rate (GFR); 25(OH)2D=1,25 dihydroxy-Vitamin D; 6MWT=Six-minute Walk Test; Q2W=every 2 weeks

^ Primary outcome of the trial. Main timepoints for trial assessments were Wk 40 (primary outcome, safety), Wk64 (additional efficacy outcomes and safety).

* Safety data for the treatment period (Weeks 0 to 64).

6.34 On the basis of direct evidence presented in the resubmission in children between ages 1 and 12 years, for every 100 patients treated with burosumab Q2W versus conventional therapy would result in:

- an approximate 1.14 and 1.02 improvement in RGI-C score and 1.34 and 1.21 improvement (reduction) in RSS score at Week 40 and Week 64, respectively.

However, it was not known whether these differences in RGI-C are clinically meaningful.

- an approximate +0.14 improvement in standing height/recumbent length (Z score) and +1.12 improvement in growth velocity of standing height/recumbent length (Z score) at Week 64. However, it was not known whether these differences in standing height/recumbent length and growth velocity are clinically meaningful.
- an approximate +46 metre improvement in 6MWT at Week 64. The mean difference in 6MWT may potentially be clinically relevant given the estimate was higher than the MCID for 6MWT of 31 metres for children.
- an approximate 0.74 mg/dL, 8.70 pg/mL, 1.25mg/dL and -146.56 U/L improvement in serum phosphorus, serum 1,25(OH)2D, phosphate reabsorption (TmP/GFR) and ALP respectively and at Week 64. However, it was not known whether these differences in biochemical outcomes are clinically meaningful.
- approximately 16 more patients experiencing any AE, 34 more patients experience treatment related AEs over 64 weeks.
- approximately 58 more patients experiencing general disorders and administration site condition, 26 more patients experiencing gastrointestinal disorders, 44 more patients experiencing respiratory, thoracic and mediastinal disorders, 25 more patients experiencing skin and subcutaneous tissue disorders, 28 more patients experiencing injury, poisoning and procedural complication and 52 more patients experiencing predefined injection site reaction TEAEs over 64 weeks.

6.35 A summary of the comparative benefits and harms for burosumab versus placebo in adult patients is presented in Table 11 below. Clinically relevant results are summarised; however, the modelled economic evaluation was based on fracture healing and WOMAC at Week 24 for adults.

Table 11: Summary of comparative benefits and harms for BUR Q4W and placebo in adults

Benefits							
LS mean change from baseline							
CL303^	**Burosumab**			**placebo**			**Mean difference (95% CI)^**
	N	**Mean Δ baseline**	**SE**	**N**	**Mean Δ baseline**	**SE**	
6MWT (m), Wk 24	68	14.8	7.67	66	-5.0	7.54	19.8 (-1.3, 40.9)
Serum phosphate (mg/dL), Wk 24	68	0.39	0.081	66	-0.01	0.067	**0.40 (0.19, 0.61)**
1,25(OH)2D (pg/mL), Wk 20	68	7.77	2.92	66	2.12	2.71	**5.7 (2.0, 9.3)**
TmP/GFR (mg/dL), Wk 24	68	0.56	0.11	66	0.13	0.09	**0.43 (0.30, 0.56)**
P1NP (ng/mL, Wk 24	68	60.93	8.62	66	-1.00	8.69	**61.9 (47.3, 76.6)**
CTx (pg/mL), Wk 24	68	207.58	51.36	66	17.33	47.26	**190.2 (109.5, 271.0)**
BALP ((µg/L), Wk 24	68	5.96	2.34	66	1.61	2.39	4.4 (-0.52, 9.2)
WOMAC physical function, Wk 24	68	-3.11	2.55	66	+1.79	2.72	-4.90 (-9.8, -0.0)
WOMAC stiffness, Wk 24	68	-7.85	3.03	66	+0.46	3.14	**-8.31 (-14.7, -1.9)**
BPI worst pain, Wk 24	68	-0.79	0.21	66	-0.32	0.22	-0.46 (-1.0, 0.08)

Proportion improved from baseline						
CL303	**Burosumab n/N**	**Placebo n/N**	**RR# (95% CI)**	**Event rate/100 patients**		**RD# (95% CI)**
				Burosumab	**Placebo**	
Active fractures/ pseudofractures healed, Wk 24	16/32	5/38	**6.60 (2.05, 21.23)**	50	13.2	**0.37 (0.16, 0.57)**

Harms (Wk 24)						
CL303	**Burosumab n/N**	**Placebo n/N**	**RR# (95% CI)**	**Event rate/100 patients***		**RD# (95% CI)**
				Burosumab	**Placebo**	
Any AEs	64/68	61/66	1.02 (0.93, 1.12)	94.1	92.4	0.02 (-0.07, 0.10)
Treatment related AEs	30/68	27/66	1.08 (0.73, 1.60)	44.1	40.9	0.03 (-0.14, 0.20)
Arthralgia	6/68	16/66	**0.36 (0.15, 0.87)**	8.8	24.2	**-0.15 (-0.28, -0.03)**
Nasopharyngitis	11/68	6/66	1.78 (0.70, 4.53)	16.2	9.1	0.07 (-0.04, 0.18)
Tooth Abscess	9/68	6/66	1.46 (0.55, 3.86)	13.2	9.1	0.04 (-0.06, 0.15)
Back pain	10/68	6/66	1.62 (0.62, 4.20)	14.7	9.1	0.06 (-0.05, 0.17)
AEs of interest: injection site reaction	8/68	8/66	0.97 (0.39, 2.43)	11.8	12.1	-0.00 (-0.11, 0.11)

Source: Compiled during the evaluation from Table 2-26, p153, Tables 2-70 to 2-73, pp158-162, Table 2-116, p229, Table 2-118, p230 and Table 2-120, p233 of the resubmission.

AE=adverse events; BALP=bone specific alkaline phosphatase; BPI=brief pain inventory; CTx=carboxy-terminal cross-linked telopeptide of type I collagen; LS=least squares; P1NP=procollagen type 1 N-propeptide; PD=pharmacodynamic; RD=risk difference; RR=risk ratio; TEAE=treatment emergent adverse event; TmP/GFR=ratio of renal tubular maximum reabsorption rate of phosphate (TmP) to glomerular filtration rate (GFR); WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index; 25(OH)2D=1,25 dihydroxy-Vitamin D; 6MWT=Six-minute Walk Test; Q4W=every 4 weeks;

^ The resubmission presented the results as LS mean (SE) difference.

* CL303 included three treatment periods: placebo-controlled treatment period (Weeks 0 to 24) and open-label treatment extension period I (to Week 96) and open-label treatment extension period II (to 149 weeks for some patients in US and EU). All patients received BUR Q4W after Week 24 to Week 96 EOS I (or Week 149 EOS II)).

Estimated during the evaluation using RevMan version 5.

6.36 On the basis of direct evidence presented in the resubmission in adults between ages 18 and 65 years, for every 100 patients treated with burosumab Q4W versus placebo would result in:

- an approximate +19.8 metre improvement in 6MWT at Week 24. However, the difference may not be clinically relevant given the estimate was below the MCID for 6MWT of 31 metres in adults.
- an approximate 0.40 mg/dL, 5.7 pg/mL and 0.43 mg/dL improvement in serum phosphorus, serum 1,25(OH)2D and phosphate reabsorption (TmP/GFR) respectively at Week 24. However, it was not known whether these differences in biochemical outcomes are clinically meaningful.
- an approximate 61.9 ng/mL, 190.2 pg/mL and 4.4 µg/L improvement in P1NP, CTx and BALP respectively at Week 24. However, it was not known whether these differences in bone biomarkers are clinically meaningful.
- an approximate -4.90, -8.31 and -0.46 improvement in WOMAC physical function, WOMAC stiffness and BPI worst pain score respectively at Week 24. The mean difference in WOMAC stiffness may not be clinically meaningful given the point estimate was below the estimated MCID for WOMAC stiffness score of 10 points.
- approximately 2 more patients experiencing any AE, 3 more patients experience treatment related AEs over 24 weeks.
- approximately 15 fewer patients experiencing arthralgia, 7 more patients experiencing nasopharyngitis, 4 more patients tooth abscess, 6 more patients experiencing back pain, and 0 patients experiencing injection site reaction AEs over 24 weeks.

Clinical claim

Paediatrics

6.37 In paediatric patients with XLH, the resubmission described burosumab as superior in terms of effectiveness and superior (and different) in terms of safety compared to conventional therapy comprising oral phosphate and active vitamin D. At the March 2021 meeting, the PBAC considered the clinical claim of superior effectiveness was reasonable; however, the claim of superior (and different) comparative safety was not adequately supported by the data (paragraphs 6.37 and 6.39, burosumab PSD, March 2021).

6.38 Overall, the PBAC again considered that the clinical claim for effectiveness of burosumab in children was supported by the clinical evidence, but noted the following issues:

- the studies were small and were limited to children aged 1-12 years, with XLH by RSS (≥ 1.5) who have received prior conventional therapy. The proposed population included paediatrics under the age of 18 years.
- although the mean difference in RGI-C and RSS at Weeks 40 and 64 were statistically significant for burosumab Q2W compared to conventional therapy,

the differences may not be clinically meaningful given the lack of established MCIDs. Patient relevant outcomes (e.g. growth, function, pain and quality of life) were secondary outcomes.

6.39 In terms of the safety claim for paediatric patients, the PBAC previously noted that although the rate of serious AEs and Grade 3 or 4 AEs were similar between burosumab and conventional therapy, burosumab was associated with more dental caries, tooth abscesses, diarrhoea and cough as well as administration site conditions such as pyrexia and that long-term use of conventional therapy is associated with nephrocalcinosis and secondary hyperparathyroidism. "Overall, the PBAC considered that burosumab had a different safety profile compared to conventional therapy with more appreciable short-term side-effects" (paragraph 7.9, burosumab PSD, March 2021). Noting that no significant new safety data were presented, the PBAC considered that the claim of superior safety in children was not supported.

Adults

6.40 In adult patients with XLH, the resubmission described burosumab as superior in terms of effectiveness and inferior (and acceptable) in terms of safety compared to placebo (and probably conventional therapy).

6.41 Overall, the PBAC considered that the clinical claim for effectiveness of burosumab in adults was supported by the clinical evidence, but noted the following issues:

- the studies were limited to patients with significant morbidity associated with XLH (e.g. BPI worst pain ≥4) who have received prior conventional therapy and were initiating burosumab treatment in adulthood. The proposed population included adults aged 18 years and above.
- although mean difference in serum PD and bone biomarkers and patient reported outcomes (WOMAC stiffness) were statistically significant at Week 24 for burosumab Q4W compared to placebo, the differences may not be clinically meaningful due to the lack of established MCIDs on PD outcomes and being below the estimated MCID for WOMAC stiffness. Improvement in fracture healing was an exploratory outcome. There was no direct evidence comparing burosumab to conventional therapy.

6.42 The PBAC considered that the claim of inferior (but acceptable) safety of burosumab compared to placebo (and probably conventional therapy) for adults was reasonable. Treatment with burosumab in adults was associated with higher incidence of nasopharyngitis, back pain, headache and tooth abscesses as well as injection site reactions in the clinical studies.

Economic analysis

6.43 The resubmission presented two separate cost utility analyses comparing burosumab and conventional therapy (oral phosphorus and calcitriol) for the treatment of XLH in children and adults. The paediatric model considered treatment of paediatric patients

who continue to receive treatment into adulthood whereas the adult model considered treatment of prevalent adult patients with established XLH. While both were Markov models, they differed in the events measured. The paediatric model (an update of the economic model presented in the March 2021 submission) was based on achievement of RSS scores, whereas the adult model (new for this resubmission) focused on clinical events such as a reduction of fractures.

Paediatrics

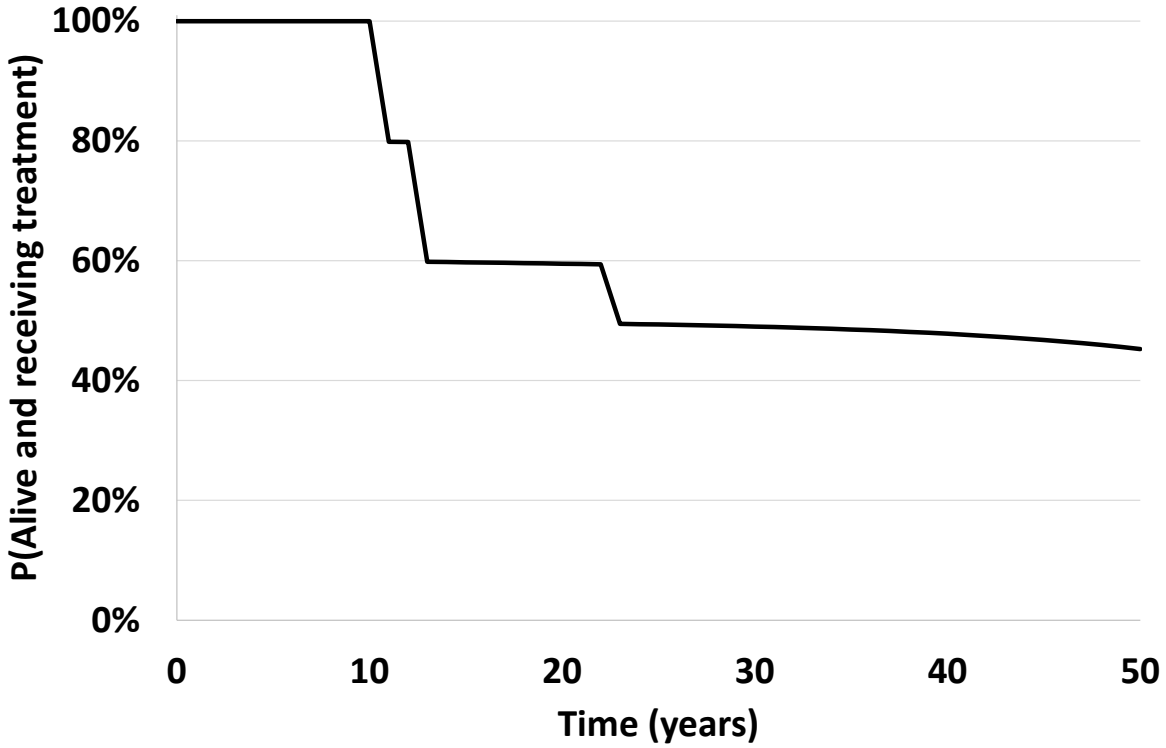
6.44 The resubmission presented an updated modelled economic evaluation comparing burosumab and conventional therapy for the treatment of XLH in children. The structure of the model was as for the March 2021 submission which was a Markov state transition model with four health states defined by RSS: Mild (RSS of 0.5 or 1.0), Moderate (RSS of 1.5 or 2.0), Severe (RSS of 2.5 or more), Healed (RSS of 0) and Death (to capture background mortality). The PBAC had previously expressed concern about the model structure, transition probabilities and RSS being the only modelled outcome and considered the base case incremental cost effectiveness ratio (ICER; $655,000 to < $755,000per additional quality adjusted life year (QALY) gained) highly uncertain and likely optimistic (paragraph 7.11, burosumab PSD, March 2021).

6.45 The PBAC's key concerns of the March 2021 economic evaluation (paragraph 7.11, burosumab PSD, March 2021) and how the resubmission addressed them are provided below:

- **Change in RSS as the only modelled outcome**. The PBAC previously considered that RSS was unlikely to capture all relevant outcomes and the inclusion of a 'healed' state was inconsistent with trial-based patient reported outcomes. The resubmission included a small survival difference between the two model arms by applying a decrement to patients receiving conventional therapy (mortality HR = 2.93 versus general population). Those receiving burosumab were assumed to follow general population mortality (which was unchanged from the March 2021 submission). This resulted in a very small difference in survival between the treatment arms and had little impact on the ICER as it occurred late in the model time horizon and therefore the effect was heavily discounted.
- **Average dose** was modelled as 0.86 mg/kg, which PBAC previously considered was likely to be low. In the resubmission, mean dose for children was increased to 0.91 mg/kg based on unpublished data from the North American Disease Monitoring Program. The ESC noted that this was lower than the mean dose received in the Early Access Program (EAP) of 1.05 mg/kg and the maximum dose in the product information (2 mg/kg).
- **Annualised transition probabilities** were constant to age 18 years, with stabilisation of disease severity from age 18, resulting in nearly all burosumab patients entering the 'healed' state by Year 10 and continuing to accrue these benefits until death. While the extrapolation of the transition probabilities

remained unchanged in the resubmission, the cost of burosumab treatment into adulthood was included, with reduced utilisation decreasing from 100% (80% from age 18 years, 60% from age 20 years, 50% from age 30-50 years). While it may be appropriate to assume treatment discontinuation over time, no evidence was provided to support the rate of discontinuation. Figure 2 demonstrates the modelled time on treatment with burosumab. In contrast to the March 2021 submission, patients who discontinued burosumab did not receive subsequent treatment with conventional therapy. If patients are likely to require conventional therapy after discontinuing burosumab, then long-term costs in the burosumab arm would be underestimated, but as the cost of conventional therapy is small compared to burosumab, the effect on the ICER would be minimal. The PSCR provided a revised base case in which utilisation in adulthood was assumed to be 90% at 18, 80% at 20 and 70% at 30 years of age).

Figure 2: Modelled time on treatment with burosumab in the paediatric model (as per resubmission)



Note: Treatment duration adjusted for survival
Source: compiled during the evaluation using the submitted model.

- The uncertainty in the extrapolation of benefits was also addressed through a reduction in the **time horizon** from 100 years in the March 2021 submission to 50 years in the resubmission versus 64 weeks of follow up data reported among CL201, CL205 and CL301. Though this was a large reduction, given limited clinical data, the model still required significant extrapolation and the ICER remained very

sensitive to time horizon. As most patients in the burosumab arm still transitioned into healed rickets by Year 10 and continued to benefit until death, the long time horizon therefore still exaggerated this uncertain transition and strongly favoured burosumab. The time horizon was further reduced to 25 years in the revised base case presented in the PSCR. The ESC considered that the revised 25 year time horizon remained long compared to the trial data and that this introduced considerable uncertainty into the model results.

- The PBAC previously considered that **burosumab's price** would need to be reduced to address the numerous uncertainties and achieve a reasonable ICER (paragraph 7.14, burosumab PSD, March 2021). The resubmission reduced the effective DPMQ of burosumab by %, equivalent to an effective AEMP of $ per 10 mg vial, $ per 20 mg vial and $ per 30 mg vial. The price was further reduced in the pre-PBAC response.

6.46 Key concerns of the economic evaluation (paragraph 7.11, burosumab PSD, March 2021) not addressed by the resubmission included:

- **Limited effectiveness data**: comparative data used in the resubmission's model were again obtained from heterogeneous sources with no data provided for children aged 13 to 17 years. Although the ESC had previously acknowledged that use of pooled data may have been reasonable considering the data available (paragraph 6.50, burosumab PSD, March 2021), ESC noted that it added considerable uncertainty to the modelling. The ESC noted that this issue remained unresolved in this resubmission.
- **Cost of harms** was again not included in the resubmission's model. The ESC noted that this issue remained unresolved.

6.47 A summary of the key components of the paediatric model and how it compared to the March 2021 submission is presented in the following table.

Table 12: Key components of the revised paediatric economic evaluation

Component	March 2021 model	Resubmission
Treatments	BUR vs conventional therapy	Unchanged. Appropriate
Type of analysis	Cost utility analysis	Unchanged. Appropriate
Outcomes	Quality-adjusted life years (QALYs) gained	Unchanged. Appropriate
Time horizon	100 years, compared with up to 64 weeks in clinical studies.	Reduced to 50 years. The model remained highly sensitive to time horizon, long-term predictions were still based on relatively short patient follow up (64 weeks). The 50 year time horizon also exaggerated the effect of favourable transition assumption of BUR treated patients into the healed rickets health state (see also transition probabilities). The time horizon was reduced to 25 years in the revised base case presented in the PSCR.
Patient population	Population was assumed to be an average age of 6.8 years at model start (based on trial data). Patients received BUR or conventional therapy continuously (assuming full compliance and no early discontinuations) until 18 years of age.	Average age at model start: unchanged. The TGA indication is for patients ≥1 years. Given the requested listing was age agnostic, as prevalent patients switch to receiving BUR treatment, mean starting age of incident patients is likely to trend towards 1 year of age (or mean age of diagnosis). Patients received BUR or conventional therapy continuously (100% compliance and no early discontinuations) until 18 years of age then continued into adulthood at reduced utilisation rates. For BUR, 80% from 18 years, 60% from 20 years, 50% from 30-50 years and 0% from 60 years. Utilisation rates into adulthood were increased in the revised base case presented in the PSCR (90% at 18 years, 80% at 20 years and 70% at 30 years of age). For conventional therapy, 71% of patients were assumed to continue treatment as adults. Note in the adult model this proportion was slightly different at 70.1%. Continuation however did not impact on the model as the model predicted almost all BUR treated patients are 'healed' of rickets by Year 10. See also transition probabilities.
Methods used to generate results	Markov state transition model	Unchanged. Reasonable.
Health states	Four chronic health states defined by Rickets Severity Score (RSS): • Mild (RSS of 0.5 or 1.0) • Moderate (RSS of 1.5 or 2.0) • Severe (RSS of 2.5 or more) • Healed (RSS of 0) An absorbing death state to account for all-cause mortality.	RSS health states and structure: unchanged. Assumed a proportional reduction in excess XLH-related mortality, applied to patients treated with BUR (extrapolated survival benefit). The survival benefit did not significantly impact results, as it occurred late in the model time horizon and therefore the effect was heavily discounted.
Cycle length	One year (with half cycle correction applied)	Unchanged. Reasonable.

Component	March 2021 model	Resubmission
Transition probabilities	• Baseline distribution of patients between health states was informed by pooled data from CL301, CL201 and CL205. • Transition probabilities in the BUR arm were also based on pooled data from these three studies reflecting change in RSS between baseline and Week 64. • Transition probabilities in the conventional therapy arm were informed by pooled data from the control arm of CL301 and a UK chart review.	Unchanged. • A single patient informed the transition probability for remaining in the 'healed' state for BUR patients, thus all BUR patients who transitioned into a 'healed' state were assumed to remain 'healed' until death. • Transition probabilities were equally applied to children of all ages up to 18 years. No data available from clinical studies to support this. • BUR treated patients can never transition to a worse health state in the model, not supported by long term data, particularly if a patient ceases treatment.
Extrapolation	• Constant annual transition probabilities up to age 18 was assumed based on Week 64 study results. • The model also assumed all patients remained in their respective RSS health state beyond age 18, thus assuming the benefit of burosumab is lifelong with a proportion of patients receiving treatment into adulthood.	Unchanged. No long-term data to support these assumptions, rendering them highly uncertain. Almost all BUR-treated patients were 'healed' of rickets by Year 10 and remained healed until death, highly favouring BUR.
Health related quality of life	Based on a Sponsor-conducted vignette study where six UK clinicians with experience in treating XLH were asked to rate vignettes of patients with XLH at the following ages: 1-4, 5-12, 13+, 18, 40 and 60 years, based on the four RSS (healed, mild, moderate, severe) health states using the EQ-5D-5L questionnaire. Utility weights were then estimated using an established algorithm using UK weights and were applied by the aforementioned age groups and RSS states in the model. No survival differences were assumed between BUR and conventional therapy, therefore, the utility values were the main driver of incremental QALY gains.	Utility values: unchanged. The current model assumed a small difference in survival outcomes between treatment groups, however, given this difference was minimal, incremental QALY gains were still largely driven by utility values.
Software package	Microsoft Excel 2019	Unchanged. Appropriate

Blue shading indicates data previously seen by the PBAC.
Source: Table 3.2, p266 of the resubmission.
BUR=burosumab; XLH=X-linked hypophosphataemia; QALY=quality adjusted life year; RSS=Rickets Severity Score.

6.48 Utilisation of conventional therapy was assumed to reduce to 71.0% for patients with persistent rickets in the conventional therapy arm from age 18. This was an increase from 59.2% receiving calcitriol and 64.6% receiving phosphorous in the March 2021 submission. The use of conventional therapy was corrected to 70.1% in the revised base case presented in the PSCR.

6.49 Patients in the 'healed' state of the conventional therapy arm received no treatment in adulthood, which was unchanged from the March 2021 submission. Adult patients

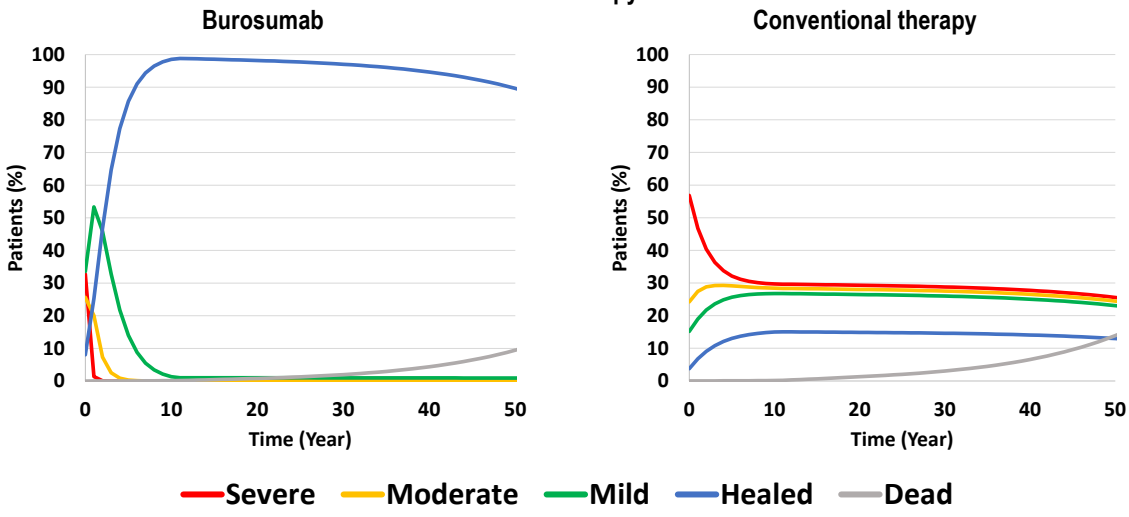
in the 'healed' state of the burosumab arm were costed to continue burosumab at the same utilisation rate as all other alive patients. The resubmission did not discuss this inconsistency in treatment in adults across the arms, but conventional therapy use in the 'healed' state would not greatly affect the ICER.

6.50 As well as the prescribed dose, the resubmission revised the age and gender specific weights used in dosing, which were taken from the Australian Paediatric Endocrine Group (APEG) growth charts for children and Australian Bureau of Statistics (ABS) National Health Survey (2017-2018) averages for adults, compared to ABS averages for both children and adults in the March 2021 submission.

6.51 Given the small difference in survival between the two treatment arms, the estimated utility values again drove the QALY results. The resubmission did not change the RSS health state utility values from the March 2021 submission. The ESC had previously considered that more reliable utility values which more appropriately reflected the health states and the likely disease progression would be required (paragraph 6.52, burosumab PSD, March 2021).

6.52 Figure 3 illustrates the Markov traces for burosumab and conventional therapy arms respectively. As with the March 2021 submission, the majority of patients in the burosumab arm achieved 'healed' RSS status by Year 10 of the model (age 17) and remain there until death, compared to conventional therapy where patients were more evenly distributed amongst the RSS states. No external validation was conducted.

Figure 3: Markov traces for burosumab and conventional therapy arms



Source: Compiled during the evaluation using Excel workbook 'Section 3.1 Workbook.xlsm', Sheet 'Trace figures'.

6.53 Key drivers of the model are presented in the following table.

Table 13: Key drivers of the paediatric model*

Description	Method/Value	Impact (PSCR base case: $455,000 to < $555,000/QALY (without SPR))
Extrapolation of clinical effect of burosumab	RSS was the only outcome extrapolated from the clinical data. • Constant annual transition probabilities for burosumab up to age 18, based on data at Week 64. • All patients remained in their respective RSS health states beyond age 18.	High, favoured burosumab. Removal of extrapolated treatment effect, assuming no further health state transitions beyond cycle 2 of the model except background mortality, the ICER increased to $755,000 to < $855,000/QALY. Including a waning effect over time by assuming a lower health state utility from 19 to 30 years of age, increased the ICER to $555,000 to < $655,000 /QALY.
Transition probabilities	• Estimated by pooling mixed data sources. • A single patient informed the transition probability for remaining in the 'healed' state for burosumab patients. • Adolescent transition probabilities were equally applied to children of all ages up to 18 years. • Burosumab treated patients can never transition to a worse health state in the model.	High, favoured burosumab.Base-case ICER almost doubled ($955,000 to < $1,055,000 /QALY) if the one patient who informed the transition to a healed state experienced mild disease instead (QALY gain significantly reduced). Annualised transition probabilities varied, as does the ICER, if alternate data used. For example, application of conventional therapy transitions increases the ICER to $855,000 to < $955,000/QALY.
Burosumab dose	Base case: 0.91 mg/kg Q2W in children; 0.95 mg/kg Q4W in adults	Moderate, favoured burosumab. Increasing the mean paediatric dose to 1.05 mg/kg (based on Australian EAP) increases ICER to $555,000 to < $655,000/QALY. Increasing the mean adult dose to 1.2 mg/kg (capped at 90mg), increases the ICER to $555,000 to < $655,000/QALY.
Burosumab utilisation in adults	Assumed that burosumab utilisation in adults reduced over time, reducing overall treatment costs (base case utilisation: 80% from 18 years, 60% from 20 years, 50% from 30-50 years, 0% from 60 years).	Moderate, favoured burosumab Applying 100% utilisation throughout adulthood, increased the ICER to $555,000 to < $655,000/QALY.

Source: compiled during evaluation.

SPR=statutory anniversary price reduction; QALY=quality adjusted life year; RSS=Rickets Severity Score; XLH=X-linked hypophosphataemia; Q2W=every two weeks; Q4W=every four weeks.

* All ICERs have been updated use the revised model provided in the PSCR

6.54 Table 14 summarises the results of the paediatric economic evaluation. The base case ICER was estimated to be $355,000 to < $455,000 per QALY gained. Total and incremental discounted QALYs were similar between the March 2021 submission and the resubmission, a direct result of minimal changes to the modelling (i.e., the only changes impacting QALYs were the introduction of survival difference and the reduction in time horizon). In comparison, despite the inclusion of burosumab treatment costs for adults, the incremental costs were greatly reduced. This was a result of the reduced effective price of burosumab and the higher percentage of patients receiving treatment in the conventional therapy arm.

6.55 The PSCR presented a revised base case in which the time horizon was decreased to 25 years, the assumed utilisation rates of burosumab into adulthood were increased and minor errors relating to the weight of female patients and use of conventional therapy were corrected. The revised base case ICER was estimated to be $455,000 to < $555,000 per QALY.

6.56 The pre-PBAC response offered a further [redacted]% reduction to the effective AEMPs of burosumab. This resulted in a revised base case ICER of $455,000 to < $555,000 per QALY.

Table 14: Results of the paediatric economic evaluation, compared to March 2021 submission

Component	March 2021			Resubmission		
	Burosumab	Conventional therapy	Incremental	Burosumab	Conventional therapy	Incremental
Total costs	$3,087,210	$47,379	$3,039,831	$[redacted]	$[redacted]	$[redacted]
Total QALYs	17.05	12.92	4.13	16.02	12.12	3.90
Incremental cost per QALY gained (without SPR)			**$736,497**			**$[redacted][1]**
Revised base case presented in the PSCR						
Total costs				$[redacted]	$[redacted]	$[redacted]
Total QALYs				12.42	9.54	2.87
Incremental cost per QALY gained						**$[redacted][2]**
Revised base case presented in the pre-PBAC response						
Total costs				$[redacted]	$[redacted]	$[redacted]
Total QALYs				12.42	9.54	2.87
Incremental cost per QALY gained						**$[redacted][2]**

Blue shading indicates data previously seen by the PBAC.

Source: Table 3-10, p136 of the March 2021 submission, Analysis worksheet of Section 3 Workbook (CEA Model), March 2021. Table 3-11, p283 of the resubmission and Analysis worksheet of Section 3.1 Workbook, March 2022 resubmission, and p4 of the PSCR

PSCR=pre-Sub-Committee response; QALY=Quality Adjusted Life Year

The redacted values correspond to the following ranges:

[1]$355,000 to < $455,000

[2]$455,000 to < $555,000

6.57 The results of sensitivity analyses for the paediatric economic evaluation are summarised below.

Table 15: Select updated results of sensitivity analyses in the paediatric model using PSCR base case

Analyses	Incremental cost	Incremental QALY	ICER
PSCR base case	**$**	**2.87**	**$**[3]
Time horizon (base case: 25 years)			
20 years	$	2.49	$[4]
15 years	$	2.00	$[4]
Burosumab dose in children (base case: 0.91 mg/kg Q2W)			
1.05 mg/kg (as per mean dosage in Australian EAP)	$	2.87	$[4]
1.2 mg/kg	$	2.87	$[4]
2 mg/kg (maximum allowable dose, capped at 90 mg)	$	2.87	$[7]
Burosumab dose in adults (base case: 0.95 mg/kg Q4W)			
2 mg/kg (capped at 90 mg)	$	2.87	$[4]
Burosumab use in adults (base case: 90% from 18 years, 80% from 20 years, 70% from 30 years)			
100% utilisation from 18 years onwards	$	2.88	$[4]
Transition probabilities for burosumab 'healed' to 'healed' state (base case: 100% based on result for 1 patient)			
(The) one patient moves to 'mild' health state	$	1.52	$[8]
Transitions same as conventional therapy	$	1.72	$[7]
Extrapolation of burosumab treatment effect (base case: assume constant transition probabilities to age 18 years)			
Removal of extrapolated transition probabilities (assuming no further health state transitions beyond cycle 2 in the model except for background mortality)	$	2.03	$[6]
Transition probabilities for conventional therapy (base case: based on CL301 and UK chart review)			
Based on CL002 study only	$	2.37	$[5]
Life time treatment effect assumption adjusted so that treatment effect wanes over time (by altering utility values) from age 19 to 30 years (base case: utility values remain constant)			
From 19 years of age, apply utilities according to the following: - Mild (base case) values to the Healed state - Moderate (base case) values to the Mild state - Severe (base case) values to the Moderate state - Applied average decrement of the above three changes to the Severe health state.	$	2.64	$[4]
Effective AEMP per vial (base case: 10 mg = $, 20 mg = $, 30 mg = $)			
Flat price of $ for 10 mg, 20 mg and 30 mg vials	$	2.87	$[1]
Flat price of $ for 10 mg, 20 mg and 30 mg vials	$	2.87	$[2]
10% reduction to base case AEMPs	$	2.87	$[3]
30% reduction to base case AEMPs	$	2.87	$[2]

Source: Updated during completion of the ESC ADV using Section 3.1 workbook PSCR.xlsm provided with the PSCR
ICER=incremental cost-effectiveness ratio; Q2W= every 2 weeks; Q4W=every 4 weeks; QALY= quality adjusted life year
The redacted values correspond to the following ranges:
[1]*$155,000 to < $255,000*
[2]*$355,000 to < $455,000*
[3]*$455,000 to < $555,000*
[4]*$555,000 to < $655,000*
[5]*$655,000 to < $755,000*
[6]*$755,000 to < $855,000*
[7]*$855,000 to < $955,000*
[8]*$955,000 to < $1,055,000*

6.58 The ESC noted that the results of the sensitivity analyses, using the revised model provided in the PSCR, indicated that the model remained sensitive to the time horizon

and the extrapolation of the burosumab treatment effect, the burosumab dose applied in children, transition probabilities and the AEMP of burosumab.

6.59 Noting that the resubmission and PSCR had addressed a number of the issues raised with the March 2021 paediatric model, the ESC considered that the revised base case ICER presented in the PSCR remained high and was likely optimistic, particularly considering the issues and uncertainties that remained relating to the burosumab dose applied, the derivation of the transition probability applied to patients remaining in the healed health state being informed by one patient and the extensive extrapolation of the trial data. The ESC considered that any further adjustments to the model should account for the uncertainties in the model structure, the assumptions applied and the lack of available data.

Adults

6.60 The resubmission presented a cost-utility analysis using Markov state transition modelling comparing burosumab and standard of care (SoC) for the treatment of prevalent adult patients with established XLH. Standard of care was assumed to be comprised of 70.1% conventional therapy (oral phosphorus and calcitriol) and 29.9% no treatment (except for symptomatic management of XLH related morbidities). The analysis was informed by data from trial CL303, online survey CL001 and expert elicitation. A summary of the model inputs is provided in the following table.

Table 16: Key components of the adult economic evaluation

Component	Description	Justification/comments
Type of analysis	Cost-utility	Reasonable
Outcomes	LYs, QALYs, costs,	Reasonable
Time horizon	25 years vs 24 weeks in CL303 (max 196 weeks for patients in extensions)	Long term extrapolation is highly uncertain as a result of the limited time frame of the trial data.
Patient population	Population was assumed to be an average age of 40 years at model start Average weight: 70.7kg, based on baseline characteristic of patients in CL303. Patients received BUR or SoC until death, with 7% discontinuation in Year 1 of BUR arm and 1% annual discontinuation from Year 2 onwards.	The model was likely to generate skewed results since it estimated results for an average patient, aged 40 and followed the patient to age 65. In practice, any patient aged 18 or over would be able to be treated with BUR. The mean weight was also less than the average adult weight assumed for the child model where 40-year olds were estimated to weigh 80.5kg and received an 80 mg dose of BUR.
Methods used to generate results	Markov state transition probabilities based on event rates converted to annual probabilities and extrapolated to 25 year.	Reasonable given data limitations.

Health states	• XLH without long-term morbidity
	• Long-term morbidity health state
	  ○ Foot fracture*
	  ○ Tibia/fibula fracture*
	  ○ Femur/pelvis fracture*
	  ○ Vertebrae/spinal fractures
	  ○ Hearing loss/tinnitus
	  ○ Requiring spinal surgery
	• Short-term morbidity event
	  ○ Requiring parathyroidectomy
	  ○ Upper limb fractures
	  ○ Other fractures
	  ○ Kidney stones
	  ○ Spinal stenosis
	  ○ Hyperparathyroidism
	  ○ Dental abscesses
	• Dead
		Patients in the alive health states who do not move to the dead state can experience a morbidity event or move to a morbidity state each cycle. Multiple morbidities can occur for each patient each cycle. Once a patient enters a morbidity state, they are assumed to stay there for the remainder of the model (i.e., accruing utility decrements associated with the morbidity each cycle). In the base case, patients in the long-term morbidity states were modelled as absorbing states and continued to accrue disutility after death. This was addressed in the revised base case presented in the PSCR.
		
		All morbidities accrue a one-off cost, and events are assumed to also accrue a utility decrement which lasts one cycle.

Cycle length	1 year	Reasonable, but may not capture shorter term morbidities.
Transition probabilities	Hawley 2020 SoC mortality HR ABS 2021 general population mortality for BUR.	BUR was assumed to revert mortality risk to that of general population. While BUR may prevent some morbidities, it was not reasonable to expect full reversal of pre-existing conditions in the adult population given its effects on rickets and growth are diminished if commencing treatment in adulthood.
Event probabilities	CL303 annual rate of fractures Expert elicitation all other morbidities General population morbidity rate assumed for BUR	Event data was highly uncertain: • CL303 collected data for a maximum 24 weeks for placebo, 196 weeks for BUR, but extrapolated to 25 years. • Expert elicitation was based on 3 questions • BUR was assumed to revert morbidity risk to that of general population.
Software package	Microsoft Excel 2019	Appropriate.

Source: compiled during the evaluation.

BUR=burosumab; HR=hazard ratio; SoC=standard of care; LYs=life years; QALYs=quality-adjusted life years

* These morbidities could occur multiple times in a lifetime. All other event rates were calculated based on a single lifetime incidence.

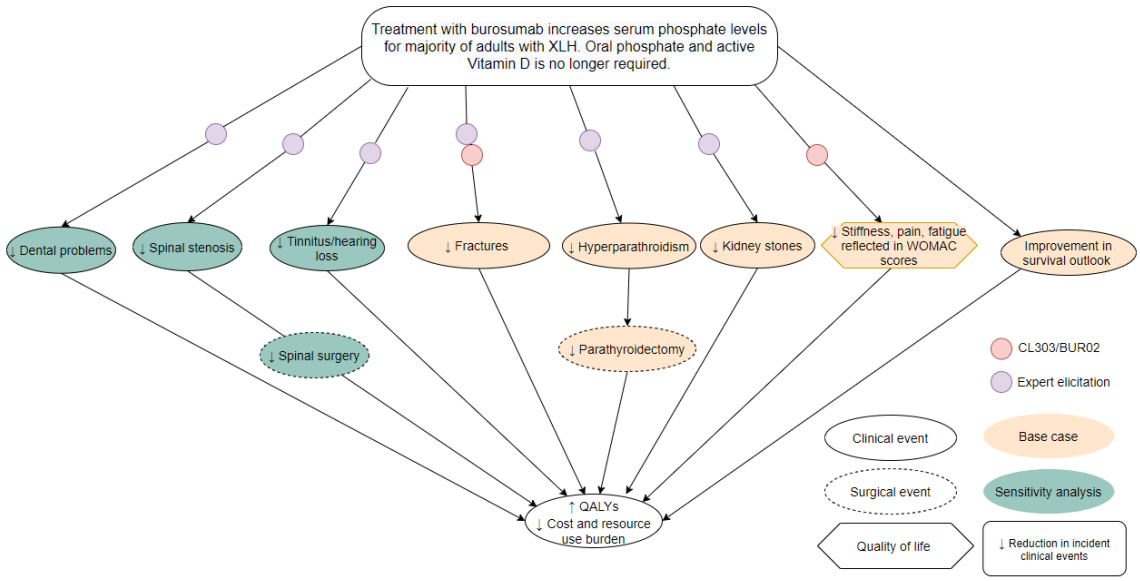
6.61 In comparison to the paediatric model, which was based on achieving RSS outcomes, the adult model focused on XLH related morbidity events and an implicit treatment utility benefit.

6.62 Multiple errors/inconsistencies were identified in the submitted Excel workbook. Correction of the errors by the evaluators resulted in a base case ICER of $355,000 to < $455,000per QALY gained, compared to $355,000 to < $455,000per QALY gained in the resubmission. The PSCR presented a revised base case in which, and in addition to other changes, the errors were corrected.

6.63 The resubmission presented a structural overview of the adult model, represented below in Figure 4. In the model, some morbidities were modelled as one-off events (e.g., upper limb fractures) whereas others were modelled as recurring health states, accruing utility decrements each cycle (e.g., tinnitus/hearing loss). Patients could be allocated to multiple morbidity states and could experience multiple different morbidity events each cycle. Transition and event probabilities were modelled independently such that the probability of morbidity related surgeries was not dependent on the probability of that morbidity. For example, in the first cycle of the model, probability of a spinal surgery was estimated to be higher than probability of spinal stenosis, demonstrating the two were not modelled sequentially as suggested by Figure 4.

6.64 Stiffness, pain and fatigue were not modelled as their own morbidity state but provided the estimate for utilities for patients not entering a morbidity health state during the cycle.

Figure 4: Overview of adult model structure



Source: Figure 3-5 of the resubmission
QALY= quality adjusted life year
All morbidities were included in the submitted base case.

6.65 The resubmission stated that a 25-year time horizon was chosen as a trade-off between the short duration of the clinical trials and the predicted lifelong impact of XLH and treatment. While XLH is a lifelong disease, the maximum follow-up from the trials was less than 4 years. The model was moderately sensitive to the time horizon.

6.66 The resubmission did not present a comparison of the trial and model populations but stated that the adult model population was based on characteristics of patients enrolled in CL303. Patients entered the model aged 40 years, with fixed mean weight 70.7kg.

6.67 Overall survival (OS) was modelled similarly to the paediatric model such that OS was assumed to equal general population survival for patients receiving burosumab and adjusted with a mortality hazard ratio of 2.93 for patients receiving SoC. Although this approach was not well justified (e.g., no trial evidence showed treatment with burosumab would result in a return to general population mortality) the ICER was minimally sensitive to mortality difference.

6.68 The resubmission stated that prevalence of morbidities in XLH by age group was converted to annual incidence either through a negative binomial model for repeating events (foot, tibia/fibula, femur/pelvis fractures) and generalised linear models for all other morbidities. The data underpinning these estimates were not presented, nor the formulas used to calculate the incidence of these morbidity events. As such the annual incidence rates could not be verified during evaluation. The resubmission did

not justify why some morbidities were expected to be repeat events and some once in a lifetime.

6.69 Patients receiving burosumab were assumed to have morbidity incidence equal to general population, and where general population data was not available incidence was assumed to be 0. Patients receiving SoC were assumed to have morbidity incidence equal to untreated XLH patients. While it may be clinically plausible that burosumab leads to a reduction in morbidities, these assumptions did not appear to be evidence-based and likely overestimated the effect of burosumab and underestimated the effect of conventional therapy.

6.70 Furthermore, the clinical effectiveness evidence presented in the resubmission was focused upon the healing of existing fractures in CL303 and did not report fractures arising during CL303. This was inconsistent with assumed benefit in the model where burosumab was assumed to prevent future morbidities, but not improve existing ones.

6.71 Some morbidities were expected to accrue lifetime utility decrements. As such the model calculated cumulative incidence for these morbidities. Since foot, tibia/fibula and femur/pelvis fractures were modelled as repeating events, patients could enter this morbidity health state multiple times and accrued an additional lifetime disutility with each entry, which was not properly adjusted for mortality. Therefore, the incidences for patients receiving SoC were significantly higher than for those receiving burosumab (e.g., equivalent of 79.3% experiencing one tibia/fibula fracture on SoC, versus 0.7% receiving burosumab). The model was very sensitive to the cumulative morbidity of these fractures. The PSCR presented a revised base case in which all recurrent events and their associated utility decrements were removed from the morbidity module of the model. The ESC considered that this was appropriate.

6.72 Mortality was unaffected by the morbidities that patients experienced, as the model assumed that overall survival implicitly captured the patients with morbidity-related deaths.

6.73 A fixed percentage of patients in the SoC arm were assumed to receive conventional therapy each cycle (70.1%), but patients on burosumab were expected to discontinue treatment at a rate of 7% in the first year and 1% every subsequent year with approximately 70% of patients were expected to be alive and receiving burosumab at the end of the time horizon. Discontinuation was much lower in the adult model than the paediatric model, which was likely reasonable given the paediatric model assumed more prior years on treatment. While treatment discontinuation was relatively low, the ICER was not very sensitive to changes in discontinuation.

6.74 As there was little difference in survival between the treatment arms, quality of life was a key driver of the results. The resubmission presented both treatment specific utilities and morbidity specific utility weights, presented in the following table.

Table 17: Utility values used in the economic evaluation

Health state	Utility	Calculation	Source of estimate
Treatment specific			
Receiving SoC (base)	0.44	Baseline	CL303 WOMAC subscores converted to EQ-5D with UK preference weights
Receiving BUR	Y1: 0.56	0.44+0.12	Difference between BUR over time and baseline of CL303 WOMAC subscores mapped to EQ-5D then added to baseline
	Y2: 0.60	0.44+0.16	
	Y3+: 0.62	0.44+0.18	
Morbidity specific			
Foot fracture Tibia/Fibula fracture Femur/Pelvis fracture (initial)	0.70	Applied one year to patients entering morbidity state	Hip fractures, from NICE TA204[1]
Foot fracture Tibia/Fibula fracture Femur/Pelvis fracture (continuing)	0.80	Applied every year to patients occupying morbidity state	Hip fractures, from NICE TA204[1]
Vertebrae/spinal fractures (initial)	0.65	Applied one year to patients entering morbidity state	Hospitalised vertebral fractures from NICE TA204[1]
Vertebrae/spinal fractures (continuing)	0.73	Applied every year to patients occupying morbidity state	Hospitalised vertebral fractures from NICE TA204[1]
Upper limb fractures	0.93	Applied one year to patients experiencing morbidity event	Wrist fracture from NICE TA204[1]
Other fractures	0.93	Applied one year to patients experiencing morbidity event	Other fracture from NICE TA204[1] (based on wrist fracture, in TA204 used for pelvis, femur, rib, clavicle, sternum, scapula, tibia and fibula fractures)
Spinal stenosis	1.00	Applied one year to patients experiencing morbidity event	Assumption
Dental abscesses	0.99	Applied one year to patients experiencing morbidity event	Claxton 2014*
Hearing loss/Tinnitus (initial)	0.92	Applied one year to patients entering morbidity state	Barton 2005*
Hearing loss/Tinnitus (continuing)	0.92	Applied every year to patients occupying morbidity state	Barton 2005*
Kidney stones	0.78	Applied one year to patients experiencing morbidity event	NICE 2019 and Pickard*
Hyperparathyroidism	1.00	Applied one year to patients experiencing morbidity event	Assumption
Requiring, parathyroidectomy	0.90	Applied one year to patients experiencing morbidity event	Symptomatic hyperparathyroidism Zanocco 2017[2]
Requiring spinal surgery (initial)	0.65	Applied one year to patients entering morbidity state	Assumed equal to vertebrae/spinal fractures (initial)
Requiring spinal surgery (continuing)	0.73	Applied every year to patients occupying morbidity state	Assumed equal to vertebrae/spinal fractures (continuing)

Source: compiled during the evaluation based on p292 of the resubmission and 'Section 3.2 Workbook.xlsm'.
BUR=burosumab; SoC=standard of care.

* Reference listed as in Excel workbook, but could not be identified/verified

[1] Denosumab for the prevention of osteoporotic fractures in postmenopausal women, October 2010, https://www.nice.org.uk/guidance/ta204

[2] Zanocco KA, Wu JX, Yeh MW. Parathyroidectomy for asymptomatic primary hyperparathyroidism: A revised cost-effectiveness analysis incorporating fracture risk reduction. Surgery. 2017 Jan;161(1):16-24.

6.75 The ESC considered that the utility data used in the adult model was highly uncertain for the following reasons:

- **Treatment specific utility data** was based on WOMAC data from CL303 mapped to the EQ-5D using Wailoo 2014, which estimated EQ-5D as a function of the pain, stiffness and function subscores. However:
  - The resubmission did not present the methods or results of this analysis.
  - Several of the WOMAC subscores were not clinically/statistically significant from baseline but resulted in statistically significant differences in the mapped EQ-5D estimates.
  - WOMAC scores (and therefore the mapped EQ-5D estimates) capture some of the disutilities associated with morbidities, especially when morbidities are associated with poor function and high amounts of pain. Therefore, morbidity utility decrements in addition to the treatment specific utilities, may represent some double counting.
- **Morbidity specific utility weights** were supposedly taken from the literature, however:
  - No full papers or complete references were provided as part of the resubmission, nor any search strategy to identify them and so very few of the sources could be identified or verified during the evaluation.
  - The choice of utility weights based on NICE TA204 was not consistent with the use of the utility weights in NICE TA204 (e.g., other fractures in NICE TA204 included fractures of the pelvis, femur, tibia and fibula, which were modelled separately in the resubmission).
  - No sources were identified specific to XLH.

6.76 Many of the treatment costs and resource used were similar to those used in the paediatric model, including disease monitoring costs and burosumab administration costs.

6.77 Drug cost per patient per year for burosumab was based on an average dose of 0.95 mg/kg every 4 weeks (based on unpublished data from North American Disease Monitoring Program), rounded to the nearest 10 mg, which resulted in a dose of 70 mg dose every 28 days. This resulted in a yearly cost of BUR of $. Patients who discontinued BUR did not receive treatment with conventional therapy.

6.78 No external validation was conducted.

6.79 Key drivers of the adult model are summarised in the following table.

Table 18: Key drivers of the adult model*

Description	Method/Value	Impact PSCR base case: $[redacted][1]/QALY (without SPR)
Treatment specific utilities	Mapped CL303 WOMAC data to EQ-5D, conventional therapy utility assumed equal to placebo arm at baseline. Utility estimates from Year 4 assumed to apply until end of time horizon.	High, favoured burosumab. A 0.03 increase in utility for patients receiving conventional therapy increased the ICER to $[redacted][1]/QALY gained. Reducing the long-term benefit of burosumab by 0.05 from Year 4 increased the ICER to $[redacted][2]/QALY gained.
Morbidity event probabilities	SoC based on data from CL303 and informed by clinical opinion BUR assumed equal to general population	High, favoured burosumab. However, the effect of the morbidity probabilities was driven by the utility weights (removal of morbidity costs from the model increase the ICER by 0.9%)
Burosumab dose	Base case: 0.95 mg/kg Q4W	High, favoured burosumab. Increasing the mean adult dose to maximum 90 mg increases ICER to $[redacted][2]/QALY gained.

Source: compiled during evaluation.
BUR=burosumab; ICER=incremental cost-effectiveness ratio; Q4W=every four weeks; QALY=quality adjusted life year; SoC=standard of care; SPR=statutory anniversary price reduction
* ICERs have been updated using the corrected revised model provided with the PSCR
The redacted values correspond to the following ranges:
[1]$555,000 to < $655,000
[2]$655,000 to < $755,000

6.80 The summary of revised base case results are presented in Table 19. The incremental QALY gain was similar to that estimated in the paediatric model (3.18 adult model, 3.90 paediatric model), though absolute QALYs were much lower.

6.81 The PSCR presented a revised base case in which all recurrent events and utility gains from the morbidity module of the model were removed and errors were corrected. An additional two errors were identified: i) morbidity costs were incorrectly adjusted for mortality as the morbidity incidences already adjusted for mortality; and ii) incorrect kidney stone costs were applied to the burosumab arm. The corrected revised base case ICER was estimated to be $555,000 to < $655,000 per QALY.

6.82 The pre-PBAC response offered a further [redacted]% reduction to the effective AEMPs of burosumab. This resulted in a revised base case ICER of $455,000 to < $550,000 per QALY.

Table 19: Results of the adult economic evaluation (discounted)

Component	BUR	SoC	Incremental
Total costs	$	$	$
Total QALYs	8.15	4.97	3.18
Incremental cost per QALY gained (without SPR)			**$**[1]
Revised base case presented in the PSCR			
Total costs	$	$	$
Total QALYs	8.28	5.84	2.44
Incremental cost per QALY gained			**$**[3]
Revised base case presented in the pre-PBAC response			
Total costs	$	$	$
Total QALYs	8.28	5.84	2.44
Incremental cost per QALY gained			**$**[2]

Source: compiled during the evaluation

QALY=Quality Adjusted Life Year; SoC=standard of care, SPR=statutory anniversary price reduction.

The redacted values correspond to the following ranges:

[1]*$355,000 to < $455,000*

[2]*$455,000 to < $555,000*

[3]*$555,000 to < $655,000*

6.83 A summary of key sensitivity analyses is presented below.

Table 20: Select updated results of sensitivity analyses in the adult model using PSCR base case

Analyses	Incremental cost	Incremental QALY	ICER
Base case	**$**	**2.44**	**$**[4]
Utilities (base case treatment SoC = 0.44, BUR Yr 1 = 0.56, Yr 2 = 0.60, Yr 3+ = 0.62, plus morbidity decrements)			
SoC w/ CT=0.47, SoC off treatment = 0.44, BUR Yr 1 = 0.56, Yr 2 = 0.60, Yr 3+ = 0.62 (placebo arm trend Evans 2021)	$	2.16	$[4]
SoC w/ CT=0.56, SoC off treatment = 0.44, BUR Yr 1 = 0.56, Yr 2 = 0.60, Yr 3+ = 0.62 (on treat CT= 1st year BUR)	$	1.37	$[6]
SoC=0.44, BUR Yr 1 = 0.56, Yr 2 = 0.60, Yr 3+ = 0.57 (Yr 3+ utility reduced by 0.05)	$	1.90	$[5]
BUR dose (base case 0.95 mg/kg to nearest 10 mg = 70 mg)			
Max dose 90 mg	$	2.44	$[5]
Patient weight (base case 70.7 kg)			
80.5 kg (as used for 40 year olds in paediatric model)	$	2.44	$[5]
Effective AEMP per vial (base case: 10 mg = $, 20 mg = $ 30 mg = $)			
Price of $ for 10 mg, 20 mg and 30 mg vials	$	2.44	$[1]
Price of $ for 10 mg, 20 mg and 30 mg vials	$	2.44	$[3]
10% reduction to base case AEMPs	$	2.44	$[3]
30% reduction to base case AEMPs	$	2.44	$[2]

Source: Updated during completion of the ESC ADV using Section 3.1 workbook PSCR.xlsm provided with the PSCR

BUR=burosumab; CI= confidence interval; CT=conventional therapy; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year; SoC=standard of care; w/=with; yr=year.

The redacted values correspond to the following ranges:

[1]*$155,000 to < $255,000*

[2]*$355,000 to < $455,000*

[3]*$455,000 to < $555,000*

[4]*$555,000 to < $655,000*

[5]*$655,000 to < $755,000*

[6]*$955,000 to < $1,055,000*

6.84 The ESC noted that the results of the sensitivity analyses, using the corrected, revised model provided in the PSCR, indicated that the model remained sensitive to baseline utility applied in the SOC arm, the dose and patient weight assumptions and the AEMP of burosumab.

6.85 Although the PSCR had addressed the issue surrounding cumulative morbidity disutilities, the ESC considered that the revised base case ICER remained high and was likely optimistic, particularly considering the issues and uncertainties that remained relating to the burosumab dose applied, the application of general population morbidity and mortality to the burosumab arm and burosumab treatment related utility gains regardless of event occurrence. The ESC considered that any further adjustments to the model should account for the uncertainties in the model structure, the assumptions applied and the lack of available data.

Drug cost/patient/year

6.86 The drug cost per patient per year for burosumab is presented below.

Table 21: Drug cost[a] per patient for burosumab for children and adults

	Paediatric model				Adult model		
	Trial CL301	Model[b]		Financials	Trial CL303	Model[c]	Financials
		Childhood	Adulthood				
Mean dose	0.87 mg/kg Q2W	0.91 mg/kg Q2W (993 mg/yr)	0.95 mg/kg Q4W (994 mg/yr)	0.91 mg/kg Q2W	1 mg/kg Q4W	0.95 mg/kg Q4W (913 mg/yr)	0.95 mg/kg Q4W
Mean total dose	-	10,913 mg	21,046 mg	-	-	18,713mg	-
Mean duration	15.14 months	10.99 yrs TH 11 yrs	21.00 yrs TH 39 yrs	NE[d]	99.9 weeks[d]	20.49 yrs TH 25 years	NE[e]
		Total 31.99 yrs TH 50 years					
Mean cost/pt/yr	-	$	$	$	-	$	$
		$					
Mean cost/pt	-	$	$	-	-	$	-
		$					

Italics indicates results calculated during the evaluation
Source: compiled during the evaluation based on Section 3.1 & 3.2 Workbooks accompanying the resubmission.
pt=patient; NE=not estimable; Q2W=every 2 weeks; Q4W=every 4 weeks; TH=time horizon; yr=year.
[a] All costs undiscounted without statutory anniversary price reductions applied. BUR dosing rounded to nearest 10mg. Administration costs for BUR not included. All treatment durations adjusted for mortality and treatment discontinuation.
[b] Paediatric model assumes uptake of 80% at age 18, 60% at age 20, 50% at ages 30-59, 0% at 60+. Mean dose differed by age: 18-34 years: 70 mg, 35-64 years:80mg, 65+ years:70mg every 28 days. Starting age is 7.
[c] Adult model assumes discontinuation rate of 7% in Year 1 and 1% every subsequent year. Mean dose based on 70mg every 28 days. Starting age is 40.
[d] The mean treatment duration for combined double-blind and open-label periods through to end of study (Week 0 to EOS II)
[e] Financials did not follow a group of initiating patients each year, rather each year the prevalent population was estimated and assumed to receive treatment for a full year

Estimated PBS usage & financial implications

6.87 This resubmission was not considered by DUSC.

6.88 As with the March 2021 submission, the resubmission estimated the financial implications using an epidemiological approach based on data of XLH prevalence from the UK General Practice Research Database Study, which was considered by the resubmission to be consistent with the Australian setting. The resubmission assumed burosumab would only substitute for conventional therapy comprising oral phosphorus and calcitriol, with a small cost-offset, and all paediatric patients and a proportion (70.1%) of adult patients commencing burosumab will continue treatment with 100% compliance.

6.89 Table 22 summarises the key inputs in the financial estimates.

Table 22: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Paediatric population aged 1-17 years		
Prevalent with XLH in paediatrics	Yr 1: 0.00233% / Yr 4: 0.00258% Yr 2: 0.00241% / Yr 5: 0.00267% Yr 3: 0.00249% / Yr 6: 0.00277% Source: UK General Practice Research Database (GPRD), Hawley 2020. The reported prevalence rate was 1.7 per 100,000 in 2014 which was extrapolated to future years assuming prevalence growth of 3.55% per year.	Based on UK data, although the resubmission noted an Australian survey (Munns 2021) which estimated the minimum local prevalence in patients <18 years was 1.31 per 100,000 persons. DUSC suggested a paediatric prevalence between 0.002 to 0.003% may be appropriate and that the prevalence of disease could increase over the forward estimates period (5.03 burosumab DUSC ADV March 2021).
Uptake of BUR in paediatrics	Yr 1: 80% / Yr 4: 96% Yr 2: 90% / Yr 5: 97% Yr 3: 95% / Yr 6: 98% Source: assumption	The assumption could not be verified. DUSC considered that the uptake rates would be higher in newly diagnosed patients versus prevalent patients (para 6.66, burosumab PSD March 2021). Sensitivity analysis indicated the estimates were not sensitive to the paediatric uptake rates.
Adult population aged ≥18 years		
Prevalence with XLH in adults	0.00133% Source: UK General Practice Research Database (GPRD), Hawley et al 2020.	May be reasonable given lack of Australian data.
Uptake of BUR in adults	Yr / Age 18-64 / Age 64-100 1 / 25% / 10% 2 / 30% / 12% 3 / 35% / 14% 4 / 40% / 16% 5 / 45% / 18% 6 / 50% / 20% Source: assumption	The assumption could not be verified. Sensitivity analysis indicated the estimates were moderately sensitive to the adult uptake rates.
BUR dose	**Paediatrics:** 0.91 mg/kg Q2W **Adults:** 0.95 mg/kg Q4W Source: Unpublished data from North American Disease Monitoring Program (DMP)	May be underestimated. The PBAC previously noted the mean dose received by children in the EAP was 1.05 mg/kg (para 7.11, burosumab PSD March 2021). For adults, CL303 reported a mean dose of BUR of 0.88-0.98 mg/kg (range: 0.2-1.5 mg/kg) at all post-baseline visits. Additional sensitivity analysis was performed during the evaluation assuming the doses above.

<table>
<tr><th>Parameter</th><th>Value applied and source</th><th>Comment</th></tr>
<tr><td>Conventional therapy dose</td><td>Paediatrics: oral phosphate: 4 x 500 mg tablets per day; and calcitriol: 2 x 0.25 mcg tablets per day
Adults: oral phosphate: 5 x 500 mg tablets per day; and calcitriol: 3 x 0.25 mcg tablets per day
Source: based on guidelines, PI, trial and expert advice.</td><td>Although the doses were consistent with the modelled economic evaluation, the application of fixed doses of oral phosphate and calcitriol was not consistent with the paediatric trial (CL301) or clinical guidelines (Haffner 2019, Carpenter 2011)#, that generally recommended weight-based dosing for phosphate (20–60 mg/kg daily given 4-6 times per day in young patients) and for calcitriol (20-30 ng/kg daily in 2-3 divided doses or 0.50 mcg daily in patients >12 months adjusted on the basis of clinical and biochemical responses). In adults, guidelines recommended phosphate 750–1,600 mg daily in 2-4 divided doses and calcitriol 0.50 to 0.75 mcg daily.</td></tr>
<tr><td>Compliance for BUR</td><td>Paediatrics: 100%
Adults: 100%
Source: assumption</td><td>This was inconsistent with the proposed continuation criteria in the restriction and with the discontinuation for adult patients assumed in the modelled economic evaluation (7% in Yr 1 and 1% Yr 2 onwards).</td></tr>
<tr><td>Compliance for conventional therapy</td><td>Paediatrics: 100%
Adults: 70.1%
Source: assumption</td><td>Reasonable. For paediatric patients, CL301 reported no discontinuations in the conventional therapy group during the 64-week treatment period. For adults. CL303 did not provide comparative evidence with conventional therapy; however, the resubmission assumed compliance for adults as patients (from CL303) who received prior conventional therapy at baseline.</td></tr>
<tr><td>Patient weight (kg)/age distribution</td><td>
<table>
<tr><th>Age</th><th>Mean weight</th><th>Age</th><th>Mean weight</th></tr>
<tr><td>1</td><td>10.48</td><td>13</td><td>46.00</td></tr>
<tr><td>2</td><td>12.74</td><td>14</td><td>50.45</td></tr>
<tr><td>3</td><td>14.24</td><td>15</td><td>53.91</td></tr>
<tr><td>4</td><td>16.72</td><td>16</td><td>57.34</td></tr>
<tr><td>5</td><td>18.24</td><td>17</td><td>60.72</td></tr>
<tr><td>6</td><td>20.74</td><td>18-24</td><td>73.15</td></tr>
<tr><td>7</td><td>17.77</td><td>25-34</td><td>77.57</td></tr>
<tr><td>8</td><td>20.77</td><td>35-44</td><td>80.50</td></tr>
<tr><td>9</td><td>28.76</td><td>45-54</td><td>82.40</td></tr>
<tr><td>10</td><td>32.52</td><td>55-64</td><td>81.40</td></tr>
<tr><td>11</td><td>36.78</td><td>65-100</td><td>78.03</td></tr>
<tr><td>12</td><td>41.52</td><td></td><td></td></tr>
</table>
Source: Australasian Paediatric Endocrine Group (APEG) growth charts for boys and girls in Australia and New Zealand. Averaged across males and females assuming gender split in paediatrics (<18 years) of 47.7% to 52.3% and in adults (≥18 years) of 35% to 65%.</td><td>Reasonable and consistent with the economic evaluation for paediatric patients. The resubmission determined the average dose of BUR treatment (rounded to nearest 10 mg) by body weight/age calculated as the mean dose multiplied by the mean body weight by age distribution in the Australian population. It is noted however, the mean weight for patients age 7 and 8 years were inconsistent with data presented in the March 2021 submission, which may be due to incorrect mean weight distribution for females age 7 and 8 years. For adult patients, the financial estimates assumed the body weight by age distribution from the general Australian adult population, which was inconsistent with the modelled economic evaluation that assumed the average patient with XLH was aged 40 years with an average weight of 70 kg based on CL303. The assumed body weight by age distribution for adults in the general population may be an overestimate given patients with XLH typically have short stature and tend to be lighter in weight.</td></tr>
</table>

<table>
<tr><th>Parameter</th><th>Value applied and source</th><th>Comment</th></tr>
<tr><td>Population weighting</td><td>
<table>
<tr><td>Age</td><td>Weighting</td><td>Age</td><td>Weighting</td></tr>
<tr><td>1</td><td>6.12%</td><td>13</td><td>5.85%</td></tr>
<tr><td>2</td><td>6.08%</td><td>14</td><td>5.78%</td></tr>
<tr><td>3</td><td>6.03%</td><td>15</td><td>5.80%</td></tr>
<tr><td>4</td><td>5.98%</td><td>16</td><td>5.77%</td></tr>
<tr><td>5</td><td>5.93%</td><td>17</td><td>5.64%</td></tr>
<tr><td>6</td><td>5.71%</td><td>18-24</td><td>11.62%</td></tr>
<tr><td>7</td><td>5.98%</td><td>25-34</td><td>19.28%</td></tr>
<tr><td>8</td><td>5.87%</td><td>35-44</td><td>17.74%</td></tr>
<tr><td>9</td><td>5.85%</td><td>45-54</td><td>15.58%</td></tr>
<tr><td>10</td><td>5.92%</td><td>55-64</td><td>14.31%</td></tr>
<tr><td>11</td><td>5.85%</td><td>65-100</td><td>21.47%</td></tr>
<tr><td>12</td><td>5.83%</td><td></td><td></td></tr>
</table>
Source: Calculated based on Y1 (2023) ABS population distribution by age (i.e., base paediatric or adult population by age / total population 1-17 years or 18-100 years)</td><td>The resubmission derived the population weighting to estimate the average number and strengths of treatment units (e.g. vials) required per dose in the population distribution by body weight/age. The resubmission inappropriately assumed the population weighting based on the Yr 1 (2023) ABS population distribution by age for all 6 years of listing. In the March 2021 meeting, DUSC noted that the pattern of use is likely to change over time; initially, prevalent patients are likely to be older and with greater disease duration; however, as the prevalent population is treated, the mean age of incident patients commencing BUR treatment is likely to be closer to 1 year of age (or age of diagnosis) (para 6.66 and 6.68, burosumab PSD March 2021).</td></tr>
<tr><td>% BUR pack split by population weight/age distribution</td><td>
<table>
<tr><td>BUR</td><td>% population split</td><td>BUR</td><td>% population split</td></tr>
<tr><td colspan="2">Paediatrics</td><td colspan="2">Adults</td></tr>
<tr><td>10mg</td><td>18.23%</td><td>10mg</td><td>52.37%</td></tr>
<tr><td>20mg</td><td>70.19%</td><td>20mg</td><td>47.63%</td></tr>
<tr><td>30mg</td><td>46.26%</td><td>30mg</td><td>200.00%</td></tr>
</table>
Source: Calculation based on Section 3. Sum of age/weight distribution (population weighting x number of BUR vials by strength)</td><td>The resubmission estimated % BUR pack split did not account for variations across the weight-based dosing and the required number of packs or strengths. Sensitivity analysis was conducted assuming average weight ±20%.</td></tr>
<tr><td>BUR scripts / year</td><td>Paediatrics: 13.04
Adults: 6.52
Source: Compliance (100%) x duration (13.04 months) x doses/month (2 for paediatrics or 1 for adults) / pack size (2)</td><td>Reasonable.</td></tr>
<tr><td>Conventional therapy scripts / year</td><td>Paediatrics: oral phosphate 14.60 and calcitriol 7.30
Adults: oral phosphate 12.80 and calcitriol 7.68
Source: Paediatrics: Compliance (100%) x duration (13.04 months) x doses/period (112 phosphate and 56 calcitriol) / pack size (100)
Adults: Compliance (70.1%) x duration (13.04 months) x doses/period (140 phosphate and 84 calcitriol) / pack size (100)</td><td>The estimates were simplistic and did not account for variations in weight-based dosing.</td></tr>
<tr><td>Substitution rate BUR : conventional therapy</td><td>1 : 1
Source: Assumption</td><td>The resubmission assumed all eligible paediatric patients and 70.1% of adult patients initiating BUR would otherwise receive conventional therapy.</td></tr>
<tr><td>MBS costs (GP visit for BUR injection)</td><td>$17.75
Source: MBS item 3 (100%)</td><td>MBS item 3 attracts 100% benefit; however, the resubmission inappropriately applied an 80% rebate on the scheduled fee. The cost of MBS item 3 was updated in the July 2021 schedule to $17.90.</td></tr>
</table>

Blue shading indicates data previously seen by the PBAC.

Source: Constructed during the evaluation from pp303-310 of the resubmission and parameters in Section 4 Workbook.xlsx.

BUR=burosumab; SC=subcutaneous; XLH=X-linked hypophosphataemia; Q2W=every 2 weeks; Q4W=every 4 weeks

Haffner D et al. 2019. Clinical practice recommendations for the diagnosis and management of X- linked hypophosphataemia: Consensus Statement. Nature Reviews Nephrology. 15(7):435-455 and Carpenter TO et al. 2011. A clinician's guide to X-linked hypophosphatemia. Journal of Bone and Mineral Research. 26(7):1381–8.

6.90 Table 23 summarises the estimated net financial impact of the proposed burosumab listing over the first six years (assumed 2023-2028).

Table 23: Estimated use and financial implications of the proposed BUR listing using effective prices[a]

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimation of number of treated patients						
Australian population (age 1-17)	[redacted]5	[redacted]5	[redacted]5	[redacted]5	[redacted]6	[redacted]6
Eligible paediatrics with XLH confirmed	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
BUR uptake rate	80%	90%	95%	96%	97%	98%
Australian population (age 18-64)	[redacted]7	[redacted]7	[redacted]7	[redacted]7	[redacted]7	[redacted]7
Eligible adults with XLH confirmed	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
BUR uptake rate	25%	30%	35%	40%	45%	50%
Australian population (age 64-100)	[redacted]5	[redacted]5	[redacted]5	[redacted]5	[redacted]5	[redacted]5
Eligible adults with XLH confirmed	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
BUR uptake rate	10%	12%	14%	16%	18%	20%
Total patients treated with BUR	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Paediatrics (age 1-17)	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Adults (age 18-100)	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Estimation of the use and financial impact of BUR#						
Total number of BUR scripts	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]3	[redacted]3
BUR 2 x 10 mg paediatrics	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
BUR 2 x 20 mgs paediatrics	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
BUR 2 x 30 mg paediatrics	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
BUR 2 x 10 mg adults	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
BUR 2 x 20 mgs adults	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
BUR 2 x 30 mg adults	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Net cost PBS/RPBS, BUR	$[redacted]9	$[redacted]10	$[redacted]10	$[redacted]10	$[redacted]10	$[redacted]11
Paediatrics (age 1-17)	$[redacted]9	$[redacted]9	$[redacted]9	$[redacted]9	$[redacted]9	$[redacted]9
Adults (age 18-100)	$[redacted]8	$[redacted]8	$[redacted]9	$[redacted]9	$[redacted]9	$[redacted]9
Estimation changes in use and financial impact of conventional therapy (oral phosphate and calcitriol)						
Total number of oral phosphate and calcitriol scripts	-[redacted]2	-[redacted]2	-[redacted]2	-[redacted]3	-[redacted]3	-[redacted]3
Net cost PBS/RPBS, oral phosphate and calcitriol	-$[redacted]8	-$[redacted]8	-$[redacted]8	-$[redacted]8	-$[redacted]8	-$[redacted]8
Paediatrics (age 1-17)	-$[redacted]8	-$[redacted]8	-$[redacted]8	-$[redacted]8	-$[redacted]8	-$[redacted]8
Adults (age 18-100)	-$[redacted]9	-$[redacted]8	-$[redacted]8	-$[redacted]8	-$[redacted]8	-$[redacted]8
Estimated financial implications for the PBS/RPBS and the health budget						
Net cost PBS/RPBS, proposed listing	$[redacted]9	$[redacted]10	$[redacted]10	$[redacted]10	$[redacted]10	$[redacted]11
Number of MBS (Item 3) services	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]4	[redacted]4
Net cost to MBS[b]	$[redacted]8	$[redacted]8	$[redacted]8	$[redacted]8	$[redacted]8	$[redacted]8
Net change to government budget[b]	$[redacted]9	$[redacted]10	$[redacted]10	$[redacted]10	$[redacted]10	$[redacted]11

Source: Tables 4-1 to 4-4, pp307-309 of the resubmission and Section 4 Workbook.xlsx.

BUR=burosumab; XLH=X-linked hypophosphataemia

a The resubmission included RPBS co-payment for paediatrics in the financial estimates.

b Corrected for MBS item 3 to receive 100% benefit and updated fee $17.90 (July 2021 MBS schedule). The resubmission applied an 80% rebate on the scheduled fee for MBS item 3 and used the previous fee $17.75 (July 2020 MBS schedule).

Corrected for mean weight-age distribution at age 7 and 8 years (i.e. 23 and 26 kg, respectively), which did not impact the base case analysis. The resubmission's mean weight for patients aged 7 and 8 was 17.77 kg and 20.77 kg, respectively

The redacted values correspond to the following ranges:

[1] < 500

[2] 500 < 5,000

[3] 5,000 to < 10,000

[4] 10,000 to < 20,000

[5]*4,000,000 to < 6,000,000*
[6]*6,000,000 to < 7,000,000*
[7]*> 10,000,000*
[8]*$0 to < $10 million*
[9]*$10 million to < $20 million*
[10]*$20 million to < $30 million*
[11]*$30 million to < $40 million*

6.91 The net cost to the PBS/RPBS was estimated to be $100 million to < $200 million (plus $0 to < $10 million net cost to MBS) over the first six years of listing. The net cost to the PBS/RPBS in the March 2021 submission for the proposed listing in paediatrics only was estimated to be $100 million to < $200 million (plus $309,700 net cost to MBS). The ESC considered that the resubmission's financial estimates were uncertain due to:

- The lack of Australian data on which to base the eligible population. Although the resubmission noted recent prevalence estimates for the Australian paediatric population (Munns et al 2021), which may be underestimated due to missing data, there were no prevalence data available for the Australian adult population.
- The lack of Australian data informing the weight distribution of patients with XLH. The assumed body weight by age distribution from the general Australian adult population may be an overestimate given patients with XLH typically have short stature and tend to be lighter in weight. It was also inconsistent with the modelled economic evaluation that assumed the average patient with XLH was aged 40 years with an average weight of 70 kg based on CL303.
- The assumption that Year 1 (2023) bodyweight/age distribution will be maintained over the first six years of listing and that age distribution of the PBS XLH population will follow that of the general population (with patient numbers evenly split across all ages 1-17 years or 18-100 years). The PBAC previously considered that there was a "likelihood that more older, and hence heavier, prevalent patients would be treated initially" (paragraph 7.12, burosumab PSD, March 2021), and that over time as the prevalent patients are treated, then incident patients commencing BUR treatment is likely to be younger with mean age closer to 1 years (or age of diagnosis) (paragraph 6.68, burosumab PSD, March 2021).
- All paediatric (age 1-17 years) and adult (age 18-100 years) patients will receive an average burosumab dose of 0.91 mg/kg Q2W and 0.95 mg/kg Q4W, respectively, which was based on unpublished North American Disease Monitoring Program. The dose likely to be used in Australian practice is uncertain. The PBAC previously noted that the mean dose received by children in the EAP was 1.05 mg/kg (paragraph 7.11, burosumab PSD, March 2021). In the main adult study, CL303, the mean dose of burosumab was 0.88-0.98 mg/kg (range: 0.2-1.5 mg/kg).
- Burosumab treatment compliance of 100% and zero attrition over time was inconsistent with the proposed continuation criteria for burosumab listing.

Financial Management – Risk Sharing Arrangements

6.92 The resubmission stated that the sponsor proposed a risk sharing arrangement (RSA) given uncertainties around the utilisation estimates and financial impact related to the eligible population, uptake rate and potential use outside the intended population or excess use or wastage of medicine. Under the RSA the sponsor would reimburse the Commonwealth 50% of any expenditure on burosumab, over and above the annual financial caps, which would be calculated based on the resubmission's base case assumptions of eligibility, uptake, and utilisation.

6.93 The ESC, noting that the PSCR stated that the main financial issues would be addressed in the pre-PBAC response, considered that a RSA which was based on revised patient estimates would be required. The PBAC noted that the pre-PBAC response did not provide revised estimates.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC did not recommend burosumab for the treatment of paediatric and adult patients with X-linked hypophosphataemia (XLH). The PBAC noted the high clinical need and strong consumer support for treatments for this condition. However, the PBAC considered that the incremental cost-effectiveness ratio (ICER) was unacceptably high at the proposed price. The PBAC considered a risk sharing arrangement (RSA) was needed to address substantial uncertainties around the financial estimates, including the impact associated with use of higher doses.

7.2 The PBAC recognised the high clinical need for effective XLH treatments and noted the strong consumer support for burosumab describing a range of benefits including the ease of administration compared to currently available therapies and the effectiveness, tolerability and improvements to quality of life associated with burosumab.

7.3 The PBAC noted that the resubmission requested a broad PBS listing for paediatric and adult patients and considered that this was appropriate.

7.4 The PBAC considered that the nominated comparator of conventional therapy, consisting of oral phosphorus and calcitriol, was appropriate for both the paediatric and adult populations.

Paediatrics

7.5 For paediatric patients, the PBAC noted that the resubmission again presented data from the randomised controlled trial CL301 and two non-comparative studies (CL201 and CL205). The PBAC noted that additional non-comparative data were presented from study KRN23-003. The PBAC noted that no longer term follow up data or data for patients aged 13 to 18 years was presented in the resubmission.

7.6 The PBAC noted that the primary outcomes presented were again the rickets severity score (RSS) and the radiographical global impression of change (RGI-C). The PBAC noted that the results of CL301 demonstrated that burosumab was associated with statistically significant changes in RSS and RGI-C at Weeks 40 and 64. The PBAC recalled that it had previously noted that these outcomes did not capture aspects of XLH which were important to patients such as changes in gross motor skills, the need for corrective surgery, pain and oral health.

7.7 The PBAC recalled that it had previously considered that clinical claim that burosumab was superior to conventional therapy in children was reasonable. The PBAC considered that this was again supported, noting the lack of data for children aged 13 to 18 years and relating to longer term follow up.

7.8 In terms of safety, the PBAC noted that the resubmission described burosumab as superior (and different) compared to conventional therapy. The PBAC recalled that it had previously considered that burosumab had a different safety profile compared to conventional therapy with more appreciable short-term side-effects. The PBAC also noted that although the rate of serious adverse events (AEs) and Grade 3 or 4 AEs were similar between burosumab and conventional therapy, burosumab was associated with more dental caries, tooth abscesses, diarrhoea and cough as well as administration site conditions such as pyrexia and that long-term use of conventional therapy is associated with nephrocalcinosis and secondary hyperparathyroidism. As no new safety data were presented in the resubmission, the PBAC therefore again considered that the claim of superior (and different) safety could not be supported.

7.9 The PBAC noted that the resubmission presented an updated cost utility analysis comparing burosumab to conventional therapy in children less than 18 years of age. The PBAC noted that although the structure was unchanged from the March 2021 economic model, a number of the PBAC's key concerns were addressed including: the inclusion of a small survival advantage for patients receiving burosumab (the original model assumed no difference), an increase in the average dose from 0.86 mg/kg to 0.91 mg/kg, reduced utilisation of burosumab in adulthood (from 100% to 80% at 18 years, 60% from 20 years and 50% from 30 to 50 years) and a reduction in the time horizon from 100 to 50 years. The PBAC noted that the ESC considered that a 50 year time horizon strongly favoured burosumab, as did the reduced utilisation of burosumab into adulthood, as only costs were impacted with discontinued patients assumed to continue to receive the utility benefits from treatment.

7.10 The PBAC noted that the PSCR presented a revised base case which further reduced the time horizon to 25 years, increased the utilisation of burosumab in adulthood to 90% at 18 years, 80% at 20 years and 70% at 30 years and corrected minor errors. This resulted in an ICER of $455,000 to < $555,000 per quality adjusted life year (QALY). The PBAC noted that the pre-PBAC response reduced the effective approved ex-manufacturer price (AEMP) of burosumab by %, resulting in an ICER of $355,000 to < $455,000 per QALY.

7.11 The PBAC noted that a number of issues and uncertainties remained in the revised model including: (i) the dose of burosumab applied (0.91 mg/kg) which was less than that received by patients in the Early Access Program of 1.05 mg/kg and the maximum dose in the Product Information (2 mg/kg); (ii) the derivation of the transition probability applied to patients remaining in the healed health state which was informed by one patient; (iii) the extrapolation of the trial data from 64 weeks to a 25-year time horizon; and (iv) the costs of harms and adverse events were not considered. Overall, the PBAC considered that the ICER presented in the pre-PBAC response remained very high and was likely underestimated.

Adults

7.12 The PBAC noted that the resubmission presented data from one randomised trial, CL303 that compared burosumab with placebo, and supportive data from six non-comparative studies. The PBAC noted that burosumab in adults was used to treat the underlying pathophysiology of the FGF23-induced hypophosphataemia and that the outcomes presented included fracture healing, biochemical markers of phosphate homeostasis and bone mineralisation, patient reported outcomes of pain, stiffness and physical functioning (WOMAC) and physical function (6MWT) which were generally consistent with the recommended clinical, biochemical and radiological follow-up assessments of adults with XLH.

7.13 The PBAC noted that there was improved healing of fractures and pseudofractures for burosumab patients in CL303, with the percentage of baseline fractures/ pseudofractures graded as fully healed at Week 24 higher in the burosumab arm (43.1%) compared to the placebo arm (7.7%). The PBAC noted that patients treated with burosumab also demonstrated improvements in serum PD biochemical and bone biomarkers, improvements in patient reported outcomes in terms of WOMAC domains and increases from baseline in 6MWT distance walked.

7.14 Overall, the PBAC considered that the claim that burosumab was superior to placebo in terms of effectiveness was supported by the data, noting the lack of long term follow up data and comparative evidence comparing burosumab with the nominated comparator.

7.15 The PBAC considered that the claim that burosumab had inferior (and acceptable) safety compared to placebo was reasonable, noting that burosumab was associated with a higher incidence of nasopharyngitis, back pain, headache and tooth abscesses.

7.16 The PBAC noted that the resubmission presented a cost utility analysis for the adult population comparing burosumab with standard of care, which comprised of 70.1% conventional therapy and 29.9% no treatment.

7.17 The PBAC noted that the PSCR presented a revised base case that corrected for a number of errors which were identified in the model during the evaluation phase and removed the accrual of disutility decrements associated with repeating morbidities.

The PBAC noted that the revised ICER was $550,000 to < $655,000 per QALY. The PBAC noted that the pre-PBAC response reduced the effective AEMP of burosumab by %, resulting in an ICER of $455,000 to < $555,000 QALY.

7.18 The PBAC considered that the ICER presented in the pre-PBAC response remained high and was likely optimistic noting that uncertainties in the model structure and assumption applied reflected the available data. In addition, the PBAC noted that a number of the model inputs likely favoured burosumab, including: (i) the application of an average burosumab dose of 0.95 mg/kg which resulted in a dose of 70 mg every four weeks which was lower than the maximum dose in the Product Information of 90 mg every four weeks; (ii) the application of general population morbidity and mortality to the burosumab arm which likely overestimated the effect of burosumab; and (iii) burosumab treatment related utility gains regardless of event occurrence.

Paediatric and adult populations

7.19 Overall, the PBAC considered that the ICERs for the paediatric and adult populations remained very high and were likely underestimated due to the inclusion of assumptions which favoured burosumab. The PBAC considered that ICERs of approximately $255,000 to < $355,000 per QALY for the paediatric and adult populations would be reasonable.

7.20 In terms of the utilisation estimates, the PBAC noted that the use of burosumab may be higher in clinical practice as there were no prevalence data available for the Australian adult population. The PBAC considered that the estimated patient numbers were conservative and reasonable in the context of a RSA.

7.21 The PBAC noted that the average dose applied for paediatric patients (0.91 mg/kg) was lower than that was received by children in the EAP (1.05 mg/kg), which may have underestimated the financial impact of listing. In addition, the PBAC noted that the estimates did not include treatment costs related to harms and adverse events (e.g. dental abscesses) and considered that the listing of burosumab on the PBS would result in an increase in the testing of PHEX mutation on the MBS.

7.22 The PBAC noted the proposed RSA which offered a [redacted]% rebate over agreed expenditure caps. The PBAC considered that due to the uncertainties in the financial estimates, particularly concerning the dose of burosumab administered, a rebate of 100% would be required.

7.23 In terms of the restriction, the PBAC noted that the Secretariat proposed a General Section 85 listing with a telephone/online authority for the initial, continuing and grandfather supplies. The PBAC considered that this was reasonable as the data to be collected at the time of prescribing could be captured by the digital service at Services Australia. The PBAC also considered that a number of the Prescriber instructions could be combined into the clinical criteria.

7.24 The PBAC considered that the change to the continuation criterion proposed in the

resubmission from "normalisation of serum phosphate levels" to "normalisation or greater than 30% improvement from pre-treatment baseline in serum phosphate levels" was not appropriate. The PBAC agreed with the ESC in considering that at 30% improvement may be uninformative for some patients, (e.g. adolescence and menopause can influence target serum levels) and in noting that the 30% threshold was based on CL303 which enrolled only adult patients (see paragraphs 3.4 and 3.5).

7.25 The PBAC considered the outstanding issues could be resolved in a simple resubmission for burosumab. The PBAC considered burosumab addresses a high and urgent unmet clinical need and was expected to provide a substantial and clinically relevant improvement in efficacy/reduction of toxicity, over the alternative therapies. Therefore, the PBAC considered an early resolution pathway would be acceptable. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation:

- A further price reduction which results in ICERs of approximately $255,000 to < $355,000 per QALY for both the paediatric and adult populations; and
- A revised RSA which offers a rebate of 100% for use over the financial impact estimates.

The early resolution resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early resolution timing is not acceptable, a standard re-entry pathway is available.

7.26 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Not recommended

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

While disappointed by the decision of the PBAC not to recommend the reimbursement of Crysvita® (burosumab) for the treatment of children and adults with X-linked hypophosphataemia (XLH), Kyowa Kirin considers the offer of an early resolution pathway to be a positive step forward.

Addendum to the March 2022 PBAC public summary document:

7.02 BUROSUMAB,

Injection 10 mg in 1 mL, Injection 20 mg in 1 mL, Injection 30 mg in 1 mL
Crysvita®
Kyowa Kirin Australia Pty Ltd®

10 Background

10.1 An early resolution submission was provided that sought to address the PBAC's concerns from its March 2022 meeting at which the PBAC did not recommend burosumab for the treatment of paediatric and adult patients with X-linked hypophosphataemia (XLH).

11 Consideration of the evidence

11.1 At its March 2022 meeting, the PBAC considered that the following outstanding issues with the burosumab resubmission could be addressed in a simple resubmission:

- A further price reduction which resulted in incremental cost effectiveness ratios (ICERs) of approximately $255,000 to < $355,000 per quality adjusted life year (QALY) for both the paediatric and adult populations would be required; and
- A revised risk sharing arrangement (RSA) which offered a rebate of 100% for use over the financial impact estimates.

11.2 The early resolution resubmission offered a price reduction for the 10, 20 and 30 mg vials, which was % lower than the effective prices offered in the original March 2021 submission. The proposed approve ex-manufacturer prices (AEMPs) were $ for 2 x 10 mg vials, $ for 2 x 20 mg vials and $ for 2 x 30 mg vials.

11.3 The incorporation of the reduced prices into the paediatric and adult models resulted in ICERs of approximately $255,000 to < $355,000 per QALY for each population (see Table 24). The ICER in the March 2022 pre-PBAC response for the paediatric population was $455,000 to < $555,000 per QALY, and for the adult population it was $455,000 to < $555,000 per QALY.

Table 24: Early resolution resubmission proposed ICERs

	Burosumb	SOC	Increment
Paediatric model			
Total costs	$	$	$
Total QALYs	12.42	9,54	2.87
ICER per QALY			$[1]
Adult model			
Total costs	$	$	$
Total QALYs	8.280	5.838	2.441
ICER per QALY			$[1]

Source: Tables 6 and 7, p5 of the early resolution resubmission
ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year; SOC = standard of care
The redacted values correspond to the following ranges:
[1]$255,000 to < $355,000

11.4 The results of incorporating the revised effective prices of burosumab into the financial impact model are presented below. The total cost over the first six years of listing was estimated to be $80 million to < $90 million, compared to $100 million to < $200 million in the March 2022 resubmission.

Table 25: Early resolution resubmission estimated financial impact

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Treated patients	[1]	[1]	[1]	[1]	[1]	[1]
Cost to PBS/RPBS	**$**[2]	**$**[3]	**$**[3]	**$**[3]	**$**[3]	**$**[3]
Cost to MBS	$	$	$	$	$	$
Net cost to Government	$[2]	$[3]	$[3]	$[3]	$[3]	$[3]
March 2022 resubmission						
Cost to PBS/RPBS	**$**[3]	**$**[4]	**$**[4]	**$**[4]	**$**[4]	**$**[5]
Cost to MBS	$	$	$	$	$	$
Net cost to Government	$[3]	$[4]	$[4]	$[4]	$[4]	$[5]

Source: Table 8, p6 of the early resolution resubmission
The redacted values correspond to the following ranges:
[1]< 500
[2]$0 to < $10 million
[3]$10 million to < $20 million
[4]$20 million to < $30 million
[5]$30 million to < $40 million

11.5 The early resolution resubmission noted that in March 2022 the PBAC suggested a RSA with a 100% rebate for any use over the financial impact estimates would be required. The sponsor advised that this was not commercially viable and proposed a revised RSA incorporating a % rebate for any use over the financial impact estimates presented above.

11.6 In terms of the proposed restriction, the early resolution resubmission requested that burosumab be listed on the PBS as a Section 100 (Highly Specialised Drugs Program [HSDP]) listing, rather than a Section 85 (General Schedule) listing as:

- XLH is a rare and complex condition which is diagnosed and managed at a limited number of specialised (mainly public hospital) treatment centres;

- Prescribing, dispensing and administration of burosumab is reasonably complex, involving weight-based dose calculations, efficient combination of vial sizes, subcutaneous injection by a healthcare provider and patient monitoring;
- Other similarly specialised rare disease medicines are listed as Section 100 (HSDP) items, such as tocilizumab for severe active juvenile idiopathic arthritis, anakinra for cryopyrin associated periodic syndromes, and ivacaftor for cystic fibrosis; and
- Listing as a Section 85 item (with associated regulated markups and margins) would preclude the sponsor from being able to meet the cost effectiveness criteria specified by PBAC for this medicine in the public summary document from the March 2022 meeting.

12 PBAC Outcome

12.1 The PBAC recommended the listing of burosumab for the treatment of patients with X-linked hypophosphataemia (XLH). The PBAC noted the high clinical need and previous strong consumer support for treatments for this condition. The PBAC considered that the incremental cost-effectiveness ratios (ICERs) for both the paediatric and adult populations were acceptable at the proposed price and that the proposed risk sharing arrangement was adequate to manage the risks associated with the uncertainties relating to the estimated financial impact to the PBS.

12.2 The PBAC noted that the incorporation of the reduced approved ex-manufacturer prices (AEMPs) for the 10, 20 and 30 mg vials into the paediatric and adult economic models resulted in ICERs of approximately $255,000 to < $355,000 per QALY. The PBAC considered that the resultant ICERs were reasonable (ICER = $255,000 to < $355,000 per QALY for the paediatric population, and ICER = $255,000 to < $355,000 per QALY for the adult population).

12.3 The PBAC noted that the incorporation of the revised effective prices of burosumab into the financial impact model resulted in a net cost to the PBS/RPBS of approximately $80 million to < $90 million over the first six years of listing. The PBAC considered that the revised financial impact of listing burosumab on the PBS was reasonable.

12.4 The PBAC considered that the proposed RSA of a [redacted]% rebate for use over the revised financial estimates was reasonable and would mitigate the risks associated with the uncertainties related to the dose of burosumab administered and the lack of prevalence data for the Australian adult XLH population, in the context of the reduced price and budget impact proposed in the resubmission.

12.5 In terms of the restriction, the PBAC considered a Section 100 – Highly Specialised Drugs Program listing was appropriate.

12.6 The PBAC recommended that burosumab should not be treated as interchangeable on an individual patient basis with any other drugs, according to s101(3BA) of the *National Health Act*.

12.7 The PBAC advised that burosumab is not suitable for prescribing by nurse practitioners.

12.8 The PBAC recommended that the Early Supply Rule should apply.

12.9 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for burosumab:

a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over conventional therapy;

b) The treatment is expected to address a high an urgent unmet clinical need as there are currently no effective treatments for this patient population; and

c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.

12.10 The PBAC noted that this submission was not eligible for an Independent Review as it is a positive recommendation.

Outcome:
Recommended

13 Recommended listing

13.1 Add new item:

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Proprietary name and manufacturer
Initial / Continuing / Grandfathered				
BUROSUMAB 10 mg in 1 mL	2	2	0	Crysvita® Kyowa Kirin Australia Pty Ltd
BUROSUMAB 20 mg in 1 mL	2	2	0	
BUROSUMAB 30 mg in 1 mL	2	2	0	

Category / program: Section 100 (Highly Specialised Drugs Program)
Prescriber type: ☒Medical Practitioners
Restriction type: ☒ Authority Required – telephone/online PBS Authorities system
Episodicity: [blank]
Severity: [blank]
Condition: X-linked hypophosphataemia
PBS Indication: X-linked hypophosphataemia

Treatment phase: Initial
Clinical criteria:
Patient must have a documented confirmation of PHEX pathogenic variant; OR
Patient must have a diagnosis of X-Linked hypophosphataemia by the presence of all of the following: (i) a serum phosphate concentration below the age adjusted lower limit of normal; (ii) current or historical (for those with growth plate fusion) radiographic X-ray evidence of rickets; (iii) elevated (or inappropriately normal) serum or plasma FGF-23 levels of above the mean of the assay-specific reference range; (iv) renal phosphate wasting demonstrated by a ratio of tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) according to age specific normal ranges using the second morning urine void and paired serum sample measuring phosphate and creatinine
Treatment criteria:
Patient must be treated by one of the following specialists: (i) paediatric endocrinologist, (ii) paediatric nephrologist, (iii) endocrinologist, or (iv) nephrologist
Administrative advice: Special Pricing Arrangements apply
Note Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Category / program: Section 100 (Highly Specialised Drugs Program)
Prescriber type: ☒Medical Practitioners
Restriction type: ☒ Authority Required – telephone/online PBS Authorities system
Episodicity: [blank]
Severity: [blank]
Condition: X-linked hypophosphataemia
PBS Indication: X-linked hypophosphataemia
Treatment phase: Continuing
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must have achieved normalisation in serum phosphate levels
AND
Clinical criteria
Patient must have radiographical evidence of stabilisation or improvement in rickets in patients without growth plate fusion
Treatment criteria:
Patient must be treated by one of the following specialists: (i) paediatric endocrinologist, (ii) paediatric nephrologist, (iii) endocrinologist, or (iv) nephrologist
Prescriber instructions:
Where adequate response to treatment with burosumab cannot be demonstrated, evidence that consideration of continuing therapy has been determined to be clinically required by a second specialist physician with expertise in the treatment of X-linked hypophosphataemia.
Administrative advice: Special Pricing Arrangements apply

Note Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Category / program: Section 100 (Highly Specialised Drugs Program)
Prescriber type: ☒Medical Practitioners
Restriction type: ☒ Authority Required – telephone/online PBS Authorities system
Episodicity: [blank]
Severity: [blank]
Condition: X-linked hypophosphataemia
PBS Indication: X-linked hypophosphataemia
Treatment phase: Grandfather
Clinical criteria:
Patient must have a documented confirmation of PHEX pathogenic variant; OR
Patient must have a confirmed diagnosis of X-Linked hypophosphataemia by the presence of all of the following: (i) a serum phosphate concentration below the age adjusted lower limit of normal; (ii) current or historical (for those with growth plate fusion) radiographic evidence of rickets; (iii) elevated (or inappropriately normal) serum or plasma FGF-23 levels of above the mean of the assay-specific reference range; (iv) renal phosphate wasting demonstrated by a ratio of tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) according to age specific normal ranges using the second morning urine void and paired serum sample measuring phosphate and creatinine
AND
Clinical criteria:
Patient must have demonstrated an adequate response to non-PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [listing date]
Treatment criteria:
Patient must be treated by one of the following specialists: (i) paediatric endocrinologist, (ii) paediatric nephrologist, (iii) endocrinologist, or (iv) nephrologist
Administrative advice: Special Pricing Arrangements apply
Administrative advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria
Note Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

14 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers

applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

15 Sponsor's Comment

Kyowa Kirin welcomes the recommendation by the Pharmaceutical Benefits Advisory Committee (PBAC) to include Crysvita® (burosumab) on the Pharmaceutical Benefits Scheme for Australians living with X-Linked Hypophosphataemia (XLH).