6.03 BUROSUMAB,
Solution for injection 10 mg in 1 mL,
Solution for injection 20 mg in 1 mL,
Solution for injection 30 mg in 1 mL,
Crysvita®,
Kyowa Kirin Australia Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested PBS Section 100 (Highly Specialised Drugs Program) Authority Required (in writing) listing for burosumab for the treatment of adult and paediatric patients with unresectable tumour induced osteomalacia (TIO), characterised by fibroblast growth factor 23 (FGF23) mediated hypophosphataemia due to tumours that cannot be curatively resected or localised.

1.2 Listing was requested on the basis of a 'frame of reference' comparison between burosumab versus conventional therapy in the TIO setting and burosumab versus conventional therapy in the X-linked hypophosphataemia (XLH) setting.

1.3 Table 1 presents the key components of the clinical issue addressed by the submission.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Patients with a confirmed diagnosis of FGF23 related hypophosphataemia in TIO associated with tumours that cannot be curatively resected or localised
Intervention	Burosumab by subcutaneous injection administered by a healthcare provider as follows: • Adults (≥18 years): Starting dose of 0.3 mg/kg rounded to the nearest 10 mg Q4W with stepwise titration as required based on serum phosphate levels up to a maximum dose of 2.0 mg/kg or 180 mg in total Q2W; • Adolescents (13–17 years): Starting dose of 0.3 mg/kg rounded to the nearest 10 mg Q2W with stepwise titration as required based on serum phosphate levels up to a maximum dose of 2.0 mg/kg or 180 mg in total Q2W; • Children (1–12 years): Starting dose of 0.4 mg/kg rounded to the nearest 10 mg Q2W with stepwise titration as required based on serum phosphate levels up to a maximum dose of 2.0 mg/kg or 90 mg in total Q2W. The maximum volume of burosumab per injection site is 1.5 mL. If multiple injections are required, they should be administered at different injection sites.
Comparator	Conventional therapy comprising: • Oral phosphorus, 20–40 mg/kg/day (1-3 g/day) divided into 4–6 daily doses; and • Oral calcitriol, 20–30 ng/kg (0.5-1.5 mcg/day) divided into 2–3 daily doses
Outcomes	Serum phosphorous levels; Histomorphometric indices; Pharmacodynamic profile; Bone turnover markers; Functional outcomes; Patient reported outcomes; Safety outcomes
Clinical claim	In people with unresectable TIO, burosumab is superior to conventional therapy in terms of efficacy and safety

Italics indicates results corrected during the evaluation.
Source: Table 1-1, p10 of the submission.
FGF23, fibroblast growth factor 23; TIO, tumour induced osteomalacia; Q4W, every 4 weeks; Q2W, every 2 weeks.

2 Background

Registration status

2.1 Burosumab was TGA registered on 6 January 2026 for the treatment of FGF23-related hypophosphataemia in tumour-induced osteomalacia associated with phosphaturic mesenchymal tumours that cannot be curatively resected or localised in adults, adolescents and children 1 year of age or older. Burosumab is also 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 listed on the PBS for the treatment of paediatric and adult patients with XLH on 1 November 2022, recommended on the basis of cost-utility analyses versus conventional therapy (oral phosphorus and active vitamin D (calcitriol)). The PBAC considered that revised ICERs for both the paediatric and adult populations were acceptable at the proposed price and that the proposed Risk Sharing Arrangement (RSA) was adequate to manage the risks associated with uncertainties in the estimated financial impact to the PBS (paragraph 12.1, burosumab Public Summary Document [PSD], March 2022 PBAC meeting with May 2022 Addendum).

2.3 The PBAC has not previously considered burosumab for the treatment of TIO.

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 and deletions are in strikethrough) is presented below.

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
BUROSUMAB					
~~burosumab 10 mg in 1 mL~~ *burosumab 10 mg/mL injection, 1 mL vial*	NEW (Public) NEW (Private)	1	1	5	Crysvita
~~burosumab 20 mg in 1 mL~~ *burosumab 20 mg/mL injection, 1 mL vial*	NEW (Public) NEW (Private)	1	1	5	
~~burosumab 30 mg in 1 mL~~ *burosumab 30 mg/mL injection, 1 mL vial*	NEW (Public) NEW (Private)	1	1	5	
Category / Program: ☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)					
Prescriber type: ☒ Medical Practitioners					
Benefit type: ☒ Authority Required ~~in writing only via OPA/post/HPOS upload~~ (*Telephone/Online PBS Authorities System)*					
Prescribing rule level:					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					

Administrative Advice: Special Pricing Arrangements apply.
Administrative Advice: 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. Monday to Friday).
Restriction Summary [new1] / Treatment of Concept: [new1A]
Indication: Tumour-induced osteomalacia
Treatment Phase: Initial *treatment* – new patient
Clinical criteria:
Patient must have a confirmed diagnosis of hypophosphataemia in tumour induced osteomalacia demonstrated by the presence of all of the following: (i) chronic clinical symptoms of fatigue, bone pain, muscle weakness and/or (pseudo) fractures; (ii) elevated (or inappropriately normal) serum or plasma FGF-23 levels above the mean of the assay-specific reference range (iii) a serum phosphate concentration below the age adjusted lower limit of normal; (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 not be a candidate for curative *surgical resection* ~~treatment~~ as a result of *either:* (i) inability to locate the causative tumour using all available functional imaging technologies; (ii) inability to completely resect the causative tumour due to size, anatomical location, or other patient contraindications or comorbidities; OR ~~(iii) persistence of hypophosphataemia symptoms despite complete surgical resection of the suspected causative tumour.~~
Patient must demonstrate persistent hypophosphatemia despite complete surgical resection of the suspected causative tumour.
Treatment criteria:
Must be treated by a medical practitioner identifying as at least one of the following specialists: (i) paediatric endocrinologist, (ii) paediatric nephrologist, (iii) endocrinologist, (iv) nephrologist.
~~**Administrative Advice**~~**: *Prescribing instructions:*** 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 4 weeks, according to the specified dosage in the approved Product Information (PI). A separate authority prescription form must be completed for each strength requested. Up to a maximum of 5 repeats will be authorised.
~~**Administrative Advice:**~~ ~~Where adequate response to treatment with this drug cannot be demonstrated, the treating physician must confirm that continuing therapy has been determined to be clinically required by a second specialist physician with expertise in the treatment of tumour induced osteomalacia.~~
~~**Administrative Advice:**~~ ***Prescribing instructions:*** Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.
Restriction Summary [new2] / Treatment of Concept: [new2A]
Episodicity: [blank]
Severity: [blank]
Condition: Tumour-induced osteomalacia
Indication: Tumour-induced osteomalacia
Treatment Phase: Continuing *treatment*
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.

Treatment criteria:
Must be treated by a medical practitioner identifying as at least one of the following specialists: (i) paediatric endocrinologist, (ii) paediatric nephrologist, (iii) endocrinologist, (iv) nephrologist.
~~**Administrative Advice:**~~ ***Prescribing instructions:***   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 4 weeks, according to the specified dosage in the approved Product Information (PI). A separate authority prescription form must be completed for each strength requested. Up to a maximum of 5 repeats will be authorised.
~~**Administrative Advice:**~~ ***Prescribing instructions:***   Where adequate response to treatment with this drug cannot be demonstrated, the treating physician must confirm that continuing therapy has been determined to be clinically required by a second specialist physician with expertise in the treatment of *this condition* ~~tumour-induced osteomalacia.~~
~~**Administrative Advice:**~~ ***Prescribing instructions:***   Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.
Restriction Summary [new3] / Treatment of Concept: [new3A]
Episodicity: [blank]
Severity: [blank]
Condition: Tumour-induced osteomalacia
Indication: Tumour-induced osteomalacia
Treatment Phase: ~~Initial – grandfather~~ *Transitioning from non-PBS to PBS-subsidised supply – 'Grandfather' arrangements*
Clinical criteria:
Patient must have previously received non-PBS-subsidised treatment with this drug for this condition *prior to [date of listing].*
AND
Clinical criteria:
Patient must have, prior to initiating treatment with this drug, a confirmed diagnosis of hypophosphataemia in tumour induced osteomalacia demonstrated by the presence of all of the following: (i) chronic clinical symptoms of fatigue, bone pain, muscle weakness and/or (pseudo) fractures; (ii) elevated (or inappropriately normal) serum or plasma FGF-23 levels above the mean of the assay-specific reference range (iii) a serum phosphate concentration below the age adjusted lower limit of normal; (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 not have been a candidate for curative surgical resection, prior to initiating treatment with this drug, as a result of either: (i) inability to locate the causative tumour using all available functional imaging technologies; (ii) inability to completely resect the causative tumour due to size, anatomical location, or other patient contraindications or comorbidities; OR
Patient must have demonstrated persistent hypophosphatemia despite complete surgical resection of the suspected causative tumour prior to initiating treatment with this drug
AND
Clinical criteria:
Patient must have achieved normalisation in serum phosphate levels.
Treatment criteria:
Must be treated by a medical practitioner identifying as at least one of the following specialists: (i) paediatric endocrinologist, (ii) paediatric nephrologist, (iii) endocrinologist, (iv) nephrologist.

~~**Administrative Advice:**~~ ***Prescribing instructions:*** 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 4 weeks, according to the specified dosage in the approved Product Information (PI). A separate authority prescription form must be completed for each strength requested. Up to a maximum of 5 repeats will be authorised.
~~**Administrative Advice:**~~ ***Prescribing instructions:*** Where adequate response to treatment with this drug cannot be demonstrated, the treating physician must confirm that continuing therapy has been determined to be clinically required by a second specialist physician with expertise in the treatment of *this condition.* ~~tumour-induced osteomalacia.~~
~~**Administrative Advice:**~~ ***Prescribing instructions:*** Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.
Prescribing Instructions: *A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.*
Administrative Advice: *This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.*

3.2 The submission proposed a Special Pricing Arrangement (SPA) that would maintain the same published and effective prices as the current PBS listing of burosumab for XLH. The submission stated that the sponsor would be receptive to any amendments to the requested restriction.

3.3 The proposed PBS indication is consistent with the approved TGA indication.

3.4 The submission proposed a Section 100 Authority Required (in writing) listing for unresectable TIO. However, the evaluation noted the authority level for XLH is telephone/electronic. The Pre-Sub-Committee Response (PSCR) agreed with the evaluation that the listing should be telephone/electronic for consistency with the XLH listing.

3.5 The requested restrictions were based on the current PBS restriction for burosumab for the treatment of XLH, modified to reflect the different diagnostic criteria for unresectable TIO. Although the definition of unresectable TIO was generally reasonable, in cases where a tumour cannot be located, expert consensus statements (Brandi et. al. 2021, Jan de Beur et al. 2022, Minisola et. al. 2023) recommend that other inherited and acquired forms of FGF23-dependent hypophosphatemia must be revisited and ruled out, including genetic testing. There was no requirement in the requested restriction to exclude differential diagnoses which may share similar clinical criteria, including any FGF-23 related hypophosphatemia (such as Fanconi syndrome, iron-infusion associated hypophosphatemia, post renal transplantation hypophosphatemia), or hereditary hypophosphataemic disorders which may be identified with genetic testing (such as XLH, hypophosphataemic rickets with hyperparathyroidism, autosomal dominant or recessive hypophosphataemic rickets, polyostotic fibrous dysplasia/McCune-Albright syndrome). The PSCR (p1) stated that the sponsor was unsure whether it would be necessary or efficient to strictly require genetic testing in order to definitively rule out hereditary causes of FGF23 related hypophosphataemia in cases of strongly suspected TIO. However, the PSCR stated, and the ESC agreed, that it may be reasonable to include wording that encourages prescribers to rule out other non-hereditary forms of the condition, such as Fanconi

syndrome, iron-infusion associated hypophosphatemia, or post renal transplantation hypophosphatemia, prior to initiating burosumab for TIO.

3.6 For continuing treatment beyond 24 weeks, the patient must have achieved normalisation in serum phosphate levels or, where an adequate response cannot be demonstrated, the treating physician must confirm that continuing treatment was clinically required by a second specialist physician. This was consistent with the restriction for XLH. Although patients with TIO had a similar average improvement in serum phosphorus level compared to XLH, fewer patients had serum phosphorus levels greater than the lower limit of normal (LLN) on average across the midpoint of the dose cycles between baseline to Week 24 (50% versus 92.6%). The PSCR (p3) noted that the extent of benefit derived from burosumab treatment in either TIO or XLH is likely to be better defined by the degree of improvement from baseline in hypophosphataemia than the proportion of patients achieving the LLN. The ESC was uncertain if it would be clinically appropriate to stop treatment with TIO if normalisation of serum phosphate levels were not achieved after 6 months, particularly given treatment with burosumab was not stopped in the CL201 study. The pre-PBAC Response (p1) agreed with ESC and stated that the intent of the restrictions is to allow patients who achieve clinical benefit to continue treatment without strict normalisation of phosphate levels. The pre-PBAC response proposed that the continuing and grandfather restrictions include a criterion stating that 'Patient must have achieved normalisation in serum phosphate levels, OR the treating physician must confirm that continuing therapy has been determined to be clinically required by a second specialist physician with expertise in the treatment of this condition'.

3.7 The PBAC noted that FGF23 testing, required under the proposed restriction, was listed on the MBS (item 66520) from 1 November 2025 to determine eligibility for a relevant treatment on the PBS (such as burosumab).[1,2]

3.8 A grandfather restriction was proposed in anticipation of a small number of patients with unresectable TIO who may be receiving burosumab through a planned compassionate access program at the time of PBS listing.

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

[1] Department of Health Disability and Ageing, (2025), 'Fact Sheet - New MBS item for FGF-23 testing for patients with a high pre-test probability of XLH for eligibility for a relevant treatment on the PBS', available from: https://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/650f3eec0dfb990fca25692100069854/48c09ae96488a340ca258cba00162c2b/$FILE/PDF%20Version%20-%20New%20Medicare%20Benefits%20Schedule%20item%20for%20Fibroblast%20growth%20factor%2023%20(FGF-23)%20testing.pdf

[2] Application No. 1778 – Fibroblast growth factor 23 (FGF-23) testing for patients with a high pre-test probability of X-linked hypophosphatemia (XLH) to determine eligibility for burosumab on the Pharmaceutical Benefits Scheme (PBS) PSD, August 2024 MSAC meeting.

4 Population and disease

4.1 TIO is an ultrarare condition caused by certain tumours that lead to low levels of phosphate in the blood (hypophosphatemia), weakening the bones over time. These tumours - most commonly benign phosphaturic mesenchymal tumours (PMTs) that can arise anywhere in the body - overproduce fibroblast growth factor 23 (FGF23). Excess FGF23 then leads to hypophosphatemia, excess loss of phosphate through urine (phosphaturia), and low or inappropriately normal $1,25(OH)_2D$ (calcitriol, an active form of Vitamin D) levels. Over time, chronic hypophosphatemia causes osteomalacia, a condition in which bones become soft, weak, and prone to breakage. Common signs and symptoms of TIO include bone pain from either the tumour or from fractures, muscle weakness, fractures, pseudofractures, height loss, chest and spinal deformation, and, in children, rickets.

4.2 Diagnosis of TIO is based on medical and family history, clinical evaluation of signs and symptoms, laboratory findings (including genetic testing if required), and imaging studies to identify and localise the underlying tumour. The ESC noted the mean age of diagnosis has been reported between 46.3 and 52.5 years and that TIO is very rare before age 18 years even though sporadic cases have been reported in children as young as age 3 years.[3,4,5]

4.3 Low serum phosphate levels, reduced tubular reabsorption of phosphate (TRP) and/or TmP/glomerular filtration rate (GFR), and high FGF23 levels are key findings that define TIO. While phosphate, TRP and TmP/GFR will be reduced in TIO, some patients may have 'normal' FGF23 levels in this context, as a result of individual ability to 'cleave' FGF23. In cases where the causative tumour cannot be located, other inherited and acquired forms of FGF23-dependent hypophosphataemia must be revisited and ruled out, including genetic testing.[6]

4.4 Surgery is first-line therapy for TIO, as complete tumour resection is curative of TIO in most cases. Successful removal of the tumour will usually normalise FGF23, phosphate and $1,25(OH)_2D$ levels within 5 days. However, in some cases, resection may not be possible due to an inability to localise the tumour, inaccessible anatomical location, threat to vital nearby structures, or contraindications or comorbidities. Resection may also be incomplete, resulting in persistent or recurrent TIO. Patients in these circumstances are considered to have unresectable TIO. In unresectable TIO, the only current treatment option ('conventional treatment') is phosphate and $1,25(OH)_2D$ supplementation. Phosphate supplements have a narrow therapeutic window

[3] Alvarez-Rivas N op. cit.
[4] Cianferotti L et. al., (2022), 'Persistence and recurrence in tumor-induced osteomalacia: A systematic review of the literature and results from a national survey/case series', Endocrine, 76(3), pp709-721. doi: 10.1007/s12020-022-03039-2.
[5] Minisola S et. al., (2023), 'Tumor-induced Osteomalacia: A Comprehensive Review', Endocrine Reviews, 44, pp 323-353. doi: 10.1210/endrev/bnac026
[6] Ibid.

requiring intensive monitoring, multiple daily doses, and are often difficult to tolerate due to gastrointestinal side effects. Long-term use of conventional therapy can also lead to renal impairment and hyperparathyroidism.[7]

4.5 Burosumab is a fully human immunoglobulin G subclass 1 (IgG1) monoclonal antibody that binds to and inhibits the biological activity of FGF23 thereby increasing renal tubular reabsorption of phosphate and serum concentration of $1,25(OH)_2D$. By targeting excess FGF23, burosumab addresses the FGF23-driven pathophysiology of TIO but does not impact the natural course of the underlying tumour. Under the proposed clinical management algorithm, burosumab would replace conventional therapy (oral phosphorous and calcitriol) for patients with unresectable TIO. Concomitant use of conventional therapy is not recommended because there is an increased risk of excess phosphate and calcium in the blood. Conventional therapy should be discontinued one week prior to initiating burosumab.

4.6 Burosumab is administered via subcutaneous (SC) injection, and dosing is based on body weight and age group (Table 2). Dose adjustment is based on response, measured by serum phosphate levels. The dosing recommendations in children and adolescents with TIO are based on pharmacokinetic (PK)/pharmacodynamic (PD) simulations extrapolated from those in adult subjects with TIO.

Table 2: Recommended dosing for burosumab in tumour induced osteomalacia

	Paediatric	**Adolescent**	**Adult**
Age range (years)	1-12	13-17	≥18
Initial weight-based dose[a]	0.4 mg/kg every 2 weeks	0.3 mg/kg every 2 weeks	0.3 mg/kg every 4 weeks
Dose increase[a] Initial increment Subsequent increments	 0.6 mg/kg 0.5 mg/kg	 0.3 mg/kg 0.2-0.5 mg/kg	 0.3 mg/kg 0.2-0.5 mg/kg
Maximum frequency of dose adjustment	Every 4 weeks	Every 4 weeks	Every 2 weeks
Serum phosphate monitoring during dose titration	Measured 4 weeks after any dose adjustment	Measured 4 weeks after any dose adjustment	Measured 2 weeks after any dose adjustment
Maximum dose[a]	2.0 mg/kg, up to 90 mg every 2 weeks	2.0 mg/kg, up to 180 mg every 2 weeks	2.0 mg/kg, up to 180 mg every 2 weeks[b]
Dose decrease	If serum phosphate is above the reference range, withhold the next dose and reassess fasting serum phosphate level in 2 weeks. Once serum phosphate is below the reference range for age, restart treatment at approximately half the previous dose, at the frequency dosed before dose interruption. If the level remains below the reference range after the re-started dose, the dose can be further adjusted.		
Dose administration	Burosumab is administered by subcutaneous injection and should be administered by a healthcare provider. The maximum volume of burosumab per injection site is 1.5 mL. As vials are available in 10 mg, 20 mg and 30 mg presentation, doses of ≥ 40 mg would require multiple injection sites.		

Source: Burosumab Draft PI, pp3-5.

a Dose rounded to the nearest 10 mg

b For patients whose serum phosphate still remains below the reference range, despite a dose of 2.0 mg/kg or 180 mg every 4 weeks, the previous dose may be divided and given every 2 weeks with incremental increases as required, up to a maximum dose of 2.0 mg/kg or 180 mg every 2 weeks.

[7] Ibid.

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

5 Comparator

5.1 The submission nominated conventional therapy as the comparator, including oral phosphorus (1 to 3 g per day, divided into 4 to 6 daily doses) and oral calcitriol (0.5 to 1.5 mcg per day, divided into 2 to 3 daily doses). The ESC considered this was appropriate, although noted that the submission did not present any efficacy or safety data for conventional therapy in unresectable TIO. The long-term compliance with conventional therapy for unresectable TIO in Australia is unknown; however, the high dosing burden and potential for adverse events (such as impaired renal function and hyperparathyroidism) may limit ongoing use.[8]

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor provided a pre-recorded hearing for this item. The recording shared a patient's lived experience with TIO and their treatment with burosumab. The patient described that they were active before the onset of the condition which was fast and caused brittle bones and fractures resulting in pain and inability to move. The patient had elevated FGF23 levels which was treated using phosphate, calcitriol and vitamin D. The patient stated that the side effects of these treatments included vomiting and an inability to eat. The patient's clinician stated that the patient also received cinacalcet to reduce their phosphate and FGF23 levels, but the side effects were unpleasant. The patient and their clinician described treatment with burosumab injections as easy, starting with a once-monthly dose. The clinician stated the patient's phosphate levels are within the normal range and their quality of life and mobility have improved. The patient stated that after beginning treatment with burosumab, they slowly started moving again and move using a walking frame. Additionally, there was a reduction pain. Overall, the clinician stated that following treatment with burosumab, the patient went from being wheelchair bound, crawling and having multiple fractures to being independent and able to look after their family. The PBAC considered that the hearing was informative as it provided a clinical and patient perspective on treating this uncommon disease.

Consumer inputs

6.2 The PBAC noted and welcomed the input from individuals (2) and an organisation (1) via the Office of Health Technology Assessment Consultation Hub.

[8] Jan de Beur S et. al., (2022), 'Global guidance for the recognition, diagnosis, and management of tumor-induced osteomalacia', Journal of Internal medicine, 293; pp309-328. doi: 10.1111/joim.13593

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6.3 Input was received from XLH Australia Inc, a consumer organisation that provides support and advocacy for individuals and families living with XLH. The organisation noted the success of burosumab in XLH and strongly supported its potential benefit for people with TIO. The input noted that people living with TIO experience a very similar disease burden as those with XLH, including severe bone pain, muscle weakness, fractures, fatigue and long delays to diagnosis. The input noted that like XLH, TIO is rare, debilitating and often life-altering, with limited effective treatment options available in Australia. The organisation noted burosumab directly targets excess FGF23, the underlying cause of tumour-induced osteomalacia, unlike current treatments which are supportive and non-specific. The input noted that access to burosumab could result in more consistent normalisation of serum phosphate levels, improved bone mineralisation and fracture healing, and reductions in bone pain, muscle weakness and fatigue. Additionally, burosumab avoids the cumulative toxicity and monitoring burden associated with high-dose oral phosphate and active vitamin D. It also reduces treatment complexity and may result in meaningful improvements in physical functioning, quality of life and long-term outcomes for people with non-resectable TIO. The input noted there is limited long-term real-world data in TIO due to the rarity of the condition, and evidence is based on small patient populations. The input also noted that some patients may experience injection-site reactions or other adverse effects, and regular monitoring is still required to assess treatment response and safety. The input noted this consideration of burosumab for TIO would represent an important step toward equity for people living with rare diseases and acknowledge that meaningful health outcomes are not solely measured by population size, but by the depth of benefit to individuals' lives. The PBAC noted that this advice was supportive of the evidence provided in the submission.

6.4 The PBAC noted both the individual inputs were not directly related to the requested indication. The PBAC advised that input from consumers is most useful when it relates directly to the indication being considered but acknowledged the value of broader perspectives in understanding community experiences with medicine.

Clinical studies

6.5 There were no head-to-head trials of burosumab versus conventional therapy for unresectable TIO. The submission was based on three small single-arm non-comparative studies of burosumab in adults with unresectable TIO (CL201, CS002 and CN007).

6.6 Details of the studies presented in the submission are provided in Table 3.

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Table 3: Studies and associated reports presented in the submission

Study ID	Protocol title/ Publication title	Publication citation
CL201 (UX023T-CL201) NCT02304367	A Phase 2 Open-Label Trial to Assess the Efficacy and Safety of KRN23, an Antibody to FGF23, in Patients with Tumour-Induced Osteomalacia (TIO) or Epidermal Nevus Syndrome (ENS)-Associated Osteomalacia. Data cutoff: 11 Jan 2019. Jan de Beur SM, Miller PD, Weber TJ, Peacock M, Insogna K, Kumar R, Rauch F, Luca D, Cimms T, Roberts MS, San Martin J, Carpenter TO. Burosumab for the Treatment of Tumor-Induced Osteomalacia.	25 Nov 2019 J Bone Miner Res. 2021 Apr;36(4):627-635.
CS002 (KRN23-002) NCT02722798	A Phase 2 Open-Label Trial to Assess the Efficacy and Safety of KRN23 in Patients with Tumour-Induced Osteomalacia or Epidermal Nevus Syndrome. Data cutoff: 3 May 2018. Imanishi Y, Ito N, Rhee Y, Takeuchi Y, Shin CS, Takahashi Y, Onuma H, Kojima M, Kanematsu M, Kanda H, Seino Y, Fukumoto S. Interim Analysis of a Phase 2 Open-Label Trial Assessing Burosumab Efficacy and Safety in Patients With Tumor-Induced Osteomalacia.	30 Oct 2018 J Bone Miner Res. 2021 Feb;36(2):262-270.
CN007 (KRN23-CN007) NCT05357573	An Open-Label, Multi Centre, Single-Cohort, Post-marketing, Phase 4 Study to Evaluate the Efficacy, Pharmacodynamics and Safety of the Anti-FGF23 Antibody, KRN23, in Adult Chinese Patients with Tumour Induced Osteomalacia (TIO). Data cutoff: 23 November 2023. Xia W, Zhang Z, Lu C, Yamaguchi S, Bai M, Yi J and Onuma H. Efficacy and Safety of Burosumab in Adult Chinese Patients with Tumor induced Osteomalacia (TIO): Analysis from an Open-Label, Multi-center, Single-cohort, Post-marketing Phase IV Study.	12 August 2024 ASBMR 2024 Annual Meeting, J Bone Miner Res 39(suppl1):105-106

Source: Table 2.2, p27 of the submission.

6.7 The key features of the studies are summarised in Table 4.

Table 4: Key features of the included evidence

Study	N	Design/ duration	Bias	Treatment	Population	Outcome(s)
CL201	14[a]	P2, MC, OL 48 wks. USA. (OL extension, results up to 300 wks). 11 Jan 2019 DCO: 144 wks follow-up	High	BUR SC 0.3 mg/kg Q4W[b]	≥18 years, unresectable TIO	1°: serum phosphorus, osteomalacia 2°: function, PD
CS002	13[c]	P2, MC, OL 144 wks[d]. Japan and Korea.	High	BUR SC 0.3 mg/kg Q4W[e]	≥18 years, unresectable TIO	1°: serum phosphorus 2°: osteomalacia, function, PD
CN007	9	P4, MC, OL 48 wks. China	High	BUR SC 0.3 mg/kg Q4W[f]	≥18 years, unresectable TIO	1°: serum phosphorus 2°: function, PD

Source: Section 2.3, pp28-31 of the submission.]

BUR, burosumab; DCO, data cutoff; MC, multi-centre; OL, open label; PD, pharmacodynamics; P2, Phase 2; P4, Phase 4; SC, subcutaneous; TIO, tumour induced osteomalacia; QxW, every x week; wk, week.

a N=14 patients had TIO. CL201 enrolled 17 patients with TIO not curable by surgical excision or epidermal nevus syndrome (ENS).

b BUR initiated at 0.3 mg/kg and titrated through Week 16, and beyond if needed, to maximum 2.0 mg/kg Q2W to achieve a fasting peak serum phosphorus level of 2.5 to 4.0 mg/dL (0.81-1.29 mmol/L).

c CS002 enrolled 14 patients, however 1 patient withdrew consent before treatment. N=13 patients received BUR treatment and were included in the analysis set.

d CSR presented final analysis at 88 weeks (DCO 3 May 2018); 112 week follow-up (DCO 18 October 2018).

e BUR initiated at 0.3 mg/kg and titrated through Week 16; Dose adjustment was allowed based on the serum phosphorus level or by the judgment of the Investigators. Dose range was from 0.1 to 2.0 mg/kg. From Week 20, BUR dose was set at the same level as at Week 16. From Week 92, BUR was administered at a dosage based on current body weight and dose.

f BUR initiated at 0.3mg/kg and titrated through Week 16 to the maximum 2.0mg/kg Q4W based on serum phosphorus levels obtained two weeks prior. From Week 20, BUR dose was set at the same level as at Week 16 and can be adjusted for optimal efficacy and safety outcomes at/after Week 20.

6.8 CL201 (N=17) and CS002 (N=14) were Phase 2, open label, multicentre and single-arm studies designed to assess the efficacy, and safety of burosumab in adult patients with

unresectable TIO or Epidermal Nevus Syndrome (ENS), in the US and Japan/Korea, respectively. However, all patients enrolled in CS002 and the majority of patients (14 of 17) enrolled in CL201 had unresectable TIO. Patients without unresectable TIO in CL201 (one patient with ENS-associated osteomalacia and two patients initially diagnosed with unresectable TIO who were diagnosed with XLH after enrolment) were excluded from the submission. CN007 (N=9) was a Phase 4 open label, multicentre and single-arm post-marketing study to assess the efficacy and safety of burosumab in adult patients with unresectable TIO in China. All studies enrolled patients with a diagnosis of TIO (or ENS in CL201 and CS002)-associated osteomalacia based on evidence of excessive FGF23 that was not amenable to cure by surgical excision of the offending tumour. Biochemical cut-offs for inclusion were serum phosphorus level < 2.5 mg/dL, serum FGF23 level ≥ 100 pg/mL, and TmP/GFR < 2.5 mg/dL. Patients with "inappropriately normal" FGF23 levels were excluded.

6.9 Burosumab dosing regimens in the included studies were largely consistent with the draft Product Information (PI). Patients received burosumab SC starting at 0.3 mg/kg every four weeks (Q4W) titrated based on serum phosphorus level to a maximum dose of 2.0 mg/kg every two weeks (Q2W) (CL201) or 2.0 mg/kg Q4W (CS002 and CN007).

6.10 Although the inclusion/exclusion criteria were generally consistent across the studies, the enrolled populations had some differences, particularly in CN007. The mean age of the CN007 population (49.6 years) was lower than in CL201 (56.9 years) and CS002 (60.5 years), as was the time since TIO diagnosis (6.5 years vs 13.7 years and 10.0 years, respectively). CN007 had a majority of male participants, while the other two studies were more balanced. The proportion of people who had received prior conventional therapy was consistent between CL201 and CS002, both almost double that observed in CN007. In the studies, eligible patients discontinued oral phosphate and active vitamin D metabolite therapy for at least 2 weeks prior to screening assessments and were not to resume supplementation for the duration of the study. The mean weight of participants differed across the three studies (94.2kg in CL201, 61.4kg in CS002 and 72.6kg in CN007). Many of these characteristics may have affected the condition's baseline severity and the response to treatment.

6.11 Overall, the ESC noted the risk of bias for CL201, CS002 and CN007 was considered high due to the nature of the study designs (very small, open label, non-comparative single arm studies). While efficacy outcomes including the assessment of biochemical PD parameters (serum phosphorus) or bone health measurements (bone biopsy histomorphometry, 99mTc bone scans, DXA and radiographs) were objective, other patient reported outcomes (pain, fatigue or physical function) or adverse events (AEs) were subjective and may be affected by reporting bias.

Comparative effectiveness

6.12 All studies measured serum phosphate/PD biochemical outcomes (as primary or secondary outcomes), as well as other outcomes, including fracture healing and physical functioning.

6.13 Table 5 presents the results of the key efficacy outcomes reported in CL201, CS002 and CN007.

Table 5: Change from baseline in serum phosphate, phosphate resorption (TmP/GFR), calcitriol ($1,25(OH)_2D$), fractures, physical function (6MWT) and patient reported outcome (BPI) in CL201, CS002 and CN007 (ITT)

Outcome	CL201 N=14[a]	CS002 N=13	CN007 N=9
Serum phosphate (mg/dL)			
Baseline, mean (SD)	1.60 (0.47)	1.62 (0.49)	1.24 (0.25)
Week 24, mean (SD)	2.33 (0.54)	2.65 (0.62)	2.67 (0.83)
Week 24, LS mean (SE) change from baseline	**0.73 (0.12)**	0.97 (0.68)[b]	1.47 (0.79)[b]
n (%) >LLN, across midpoint of dose cycles (Week 0-24)	7 (50)	9 (69.2)	-
Week 48, mean (SD)	2.53 (0.62)	2.70 (0.44)	3.00 (0.86)
Week 48, LS mean (SE) change from baseline	**0.89 (0.17)**	0.99 (0.48)[b]	1.74 (0.94)[b]
n (%) >LLN, across end of dose cycles (Week 0-48)	-	6 (46.2)[c]	6 (66.7)
Week 144, mean (SD)	2.56 (0.62)	-	-
Week 144, LS mean (SE) change from baseline	**1.02 (0.21)**	-	-
TmP/GFR (mg/dL)			
Baseline, mean (SD)	1.12 (0.54)	1.15 (0.43)	0.81 (0.28)
Week 24, mean (SD)	1.87 (0.55)	2.30 (0.71)	2.58 (1.13)
Week 24, LS mean (SE) change from baseline	**0.79 (0.13)**	1.14 (0.79)[b]	1.78 (1.11)[b]
Week 48, mean (SD)	2.12 (0.64)	2.30 (0.48)	2.80 (0.85)
Week 48, LS mean (SE) change from baseline	**0.87 (0.14)**	1.08 (0.65)[b]	1.93 (0.97)[b]
Week 144, mean (SD)	2.18 (0.67)	-	-
Week 144, LS mean (SE) change from baseline	**1.05 (0.23)**	-	-
$1,25(OH)_2D$ (pg/mL)			
Baseline, mean (SD)	25.9 (8.78)	22.58 (11.87)	-
Week 24, mean (SD)	39.9 (15.53)	45.29 (12.83)	-
Week 24, LS mean (SE) change from baseline	**9.86 (4.13)**	21.84 (15.76)[b]	-
Week 48, mean (SD)	44.3 (22.96)	49.29 (10.89)	-
Week 48, LS mean (SE) change from baseline	**10.45 (4.85)**	26.37 (13.71)[b]	-
Week 144, mean (SD)	32.0 (12.49)	-	-
Week 144, LS mean (SE) change from baseline	0.97 (2.59)	-	-
Total active fractures/pseudofractures (99mTc-labelled bone scan)			
Baseline, n	249	164	68
Week 24 grade, n (% baseline)			
Healed	3 (1.2)	2 (1.2)	0
Partially healed	40 (16.1)	8 (4.9)	11 (16.2)
New findings	19	1	2
Week 48 grade. n (% baseline)			
Healed	18 (7.2)	24 (14.6)	1 (1.5)
Partially healed	64 (25.7)	28 (17.1)	23 (33.8)
New findings	17	0	0
Week 144 grade. n (% baseline)			
Healed	81 (32.5)	-	-
Partially healed	32 (12.9)	-	-
New findings	3	-	
6MWT (metres walked)			
Baseline, mean (SD)	309.0 (210.5)	295.8 (96.0)	199.2 (123.3)
Week 24, mean (SD)	334.1 (183.9)	329.2 (115.0)	303.7 (161.5)
Week 24, LS mean (SE) change from baseline	19.5 (15.6)[c]	33.0 (44.8)[b]	104.5 (159.9)[b]
Week 48, mean (SD)	331.4 (174.7)	353.7 (115.8)	361.5 (162.3)
Week 48, mean (SE) change from baseline	25.5 (16.6)[c]	57.5 (42.8)[b]	162.6 (152.7)[b]
BPI-Q3 (Worst Pain)			

Outcome	CL201 N=14[a]	CS002 N=13	CN007 N=9
Baseline, mean (SD)	5.0 (3.2)	4.4 (2.6)	4.9 (3.2)
Week 24, mean (SD) Week 24, LS mean (SE) change from baseline	4.5 (3.1) -0.55 (0.69)[c]	3.0 (2.7) -1.3 (1.7)[d]	4.0 (2.3) −0.6 (3.5)[d]
Week 48, mean (SD) Week 48, mean (SE) change from baseline	4.1 (3.1) -0.90 (0.73)[c]	2.9 (2.9) -1.3 (2.8)[d]	2.7 (2.8) −2.6 (2.8)[d]
Week 144, mean (SD) Week 144, mean (SE) change from baseline	4.1 (2.7) -0.98 (0.64)[c]	- -	- -
BPI Pain Severity			
Baseline, mean (SD)	3.9 (2.6)	3.1 (2.3)	3.6 (2.6)
Week 24, mean (SD) Week 24, LS mean (SE) change from baseline	3.5 (2.6) -0.49 (0.62)[c]	2.2 (2.0) -0.83 (1.6)[d]	2.7 (2.3) -0.7 (3.3)[d]
Week 48, mean (SD) Week 48, mean (SE) change from baseline	3.0 (2.6) -0.85 (0.67)[c]	2.5 (2.4) -0.52 (1.9)[d]	1.9 (1.91) -2.0 (2.7)[d]
Week 144, mean (SD) Week 144, mean (SE) change from baseline	3.1 (1.9) **-0.94 (0.41)[c]**	- -	- -

Bold text indicates statistical significance.

Source: Table 2-17, p44, Table 2-18, p46, Table 2-25, p54, Table2-26, p56 of the submission, Table 14.2.1.1.1.1.4, pp514-518, Table 14.2.1.1.3.1.4, pp562-566 of CL201 CSR.pdf; Table 14.2.1-1, pp127-130, Table 14.2.1-2, p131, Table 14.2.1-8, pp140-150, Table 14.2.1-7, pp139-140, Table 14.2.1-12, p190 of CS002 CSR.pdf, Table 14.2.2.4, pp168-181, Table 14.2.7.5, pp290-291 of CN007 CSR.pdf.

BPI, Brief Pain Inventory; ENS, epidermal nevus syndrome; ITT, intention-to-treat; LLN, lower limit of normal; PD, pharmacodynamic; TIO, tumour induced osteomalacia; TmP/GFR, ratio of renal tubular maximum reabsorption rate of phosphate (TmP) to glomerular filtration rate (GFR); XLH, X-Linked hypophosphataemia; $25(OH)_2D$, 1,25 dihydroxy-Vitamin D; 6MWT, 6-minute walk test.

Note: LLN was 2.5 mg/dL (0.81 mmol/L) in CL201, CS002 and CN007.

a TIO analysis set included the patients with TIO (N=14) who received at least one dose of study drug. It excluded two patients with XLH and one patient with ENS-associated osteomalacia who were in the ITT.

b Reported as mean (SD).

c The GEE model included the change from baseline as the dependent variable, time as the categorical variable and adjusted for baseline measurement, with compound symmetry covariance structure.

d Reported as mean change (SD) from baseline.

6.14 Compared to baseline, the ESC noted the studies showed patients treated with burosumab had improved serum phosphorus levels, improved phosphate resorption (TmP/GFR) and improved serum calcitriol ($1,25(OH)_2D$) at Week 24, and the average improvement remained similar at later time points. Approximately 50–69% of patients achieved mean serum phosphorus above the LLN (2.5 mg/dL) across the midpoint of dose cycles from baseline to Week 24 (CL201 and CS002), when treatment response would be assessed under the proposed PBS restriction (see paragraph 3.6). Other outcomes also showed improvement over time, including the proportion of healed and partially healed fractures, self-reported pain scores and the 6-minute walk test (6MWT).

6.15 The submission presented additional evidence from real-world studies with burosumab, conventional therapy and surgical treatments for TIO. These included a study by Cardiou 2025[9] using data from the French Early Access Program to burosumab in patients with TIO aged ≥1 years between July 2022 and December 2023. The TIO Data Monitoring Program snapshot analysis (18 June 2024) was based on data

[9] Cadiou S et. al., (2025), 'Real-world efficacy and safety of burosumab in tumor-induced osteomalacia: case series from an early access program', JBMR Plus, 9(6):ziaf039. doi: 10.1093/jbmrpl/ziaf039.

from a 10-year prospective, observational study enrolling adult and paediatric patients with TIO from approximately 17 sites across the US, Canada and Latin America (including patients previously enrolled in CL201). The submission also included 12 published case reports/series of burosumab treatment in unresectable TIO in adults aged 41 to 77 years. Overall, the real-world evidence was broadly consistent with the results from the main clinical studies presented in the submission. Patients treated with burosumab generally experienced improved PD/biochemical outcomes (serum phosphorus, although not all patients achieved the targeted threshold of >LLN) and patient reported outcomes (pain, fatigue, physical function and quality of life).

Comparative harms

6.16 Table 6 summaries the key AEs for the treatment period to Week 144 for CL201, Week 88 for CS002 and Week 48 for CN007.

Table 6: Summary of key adverse events in CL201, CS002 and CN007

TEAEs	CL201 Week 144	CS002 Week 88	CN007 Week 48
	N=14	N=13	N=9
Any TEAEs	14 (100)	12 (92.3)	9 (100)
Serious TEAEs	7 (50.0)	3 (23.1)	0 (0)
Related TEAEs	9 (64.3)	5 (38.5)	3 (33.3)
Grade 3 or 4 AEs	7 (50.0)	3 (23.1)	NR
Treatment discontinuation due to TEAEs	1 (7.1)	0 (0)	0 (0)
Study discontinuation due to TEAEs	0 (0.0)	0 (0)	0 (0)
Death	1 (7.1)	0 (0)	0 (0)
General disorders and administration site conditions	9 (64.3)	4 (30.8)	2 (22.2)
Gastrointestinal disorders	10 (71.4)	6 (46.2)	NR
Infections and infestations	13 (92.9)	10 (76.9)	6 (66.7)
Respiratory, thoracic and mediastinal disorders	10 (71.4)	2 (15.4)	3 (33.3)
Musculoskeletal and connective tissue disorders	14 (100)	8 (61.5)	3 (33.3)
Metabolism and nutrition disorders	7 (50.0)	1 (7.7)	6 (66.7)
Nervous system disorders	6 (42.9)	6 (46.2)	NR
Skin and subcutaneous tissue disorders	4 (28.6)	4 (30.8)	NR
Injury, poisoning and procedural complications	11 (78.6)	6 (46.2)	NR
Predefined injection site reaction TEAEs	3 (21.4)	1 (7.7)	NR

Source: Tables 2-31, p60; Table 2-34, p62; Table 2-35, p64; Table 2-38, p66 of the submission; Table 14.3.1.2.4, pp2431-2446, CL201 CSR; Table 14.3.1-3.1, pp298-300, CS002 CSR; Table 14.3.1.3.1, pp334-336, CN007 CSR.
NR, not reported; TEAE, treatment emergent adverse event.

6.17 Almost all patients in the included studies experienced a TEAE. Frequently experienced TEAEs were pain in the extremity, arthralgia, musculoskeletal pain, back pain, muscle spasms, upper respiratory tract infection, nasopharyngitis, diarrhoea, nausea, and vomiting. The TGA Delegate's Overview requested incorporating descriptions of hypersensitivity (rash, drug eruption and hypersensitivity) and restless leg syndrome under 'Description of selected adverse reactions in adults with TIO', as they are pertinent and significant.

Benefits/harms

6.18 A benefits and harms table was not presented as the available evidence did not allow for a study-based comparison of effectiveness and safety between burosumab and conventional therapy.

Clinical claim

6.19 The submission described burosumab as superior in terms of effectiveness and safety compared to conventional therapy (oral phosphorus and calcitriol).

6.20 Overall, the ESC considered the clinical claim of superior effectiveness was likely reasonable, despite the absence of comparative evidence versus conventional therapy, as well as substantial uncertainties and evidence gaps (e.g., no clinical data in paediatric patients). The three small single-arm studies presented in the submission found that, on average, adults treated with burosumab showed significant improvements from baseline in serum phosphate levels and other outcomes by Week 24, and that these improvements were maintained up to Week 144. Although the relative effectiveness versus conventional therapy for unresectable TIO was unknown, the PBAC had previously accepted that burosumab was superior to conventional therapy for XLH based on head-to-head evidence in paediatric patients (paragraphs 6.38 and 6.41, burosumab PSD, March 2022 PBAC meeting with May 2022 Addendum).

6.21 In contrast, the ESC considered the claim of superior safety may not be reasonable. Patients treated with burosumab in the included studies experienced injection site reactions (21% in CL201 and 8% in CS002), which do not arise with orally administered conventional therapy. Other treatment emergent adverse events were also very common (see Table 6). Based on the comparative evidence presented in the submission for XLH, the PBAC previously considered that burosumab had more appreciable short-term side-effects such as dental caries, tooth abscesses, diarrhoea, cough and administration site reactions, whereas long-term use of conventional therapy was associated with nephroacalcinosis and secondary hyperparathyroidism. The PSCR (p2) claimed the safety profile of burosumab in TIO is predictable, manageable and acceptable, noting (i) the most frequently reported adverse events in the clinical studies were related either to the method of administration or the underlying disease condition, and (ii) that no serious adverse events reported in any of the studies were considered to be related to burosumab treatment. Additionally, the PSCR argued that the safety profile of conventional therapy is generally known to be significantly more problematic, with serious side effects of nephrocalcinosis, reduced kidney function, and hyperparathyroidism being reasonably common and were an important limitation on treatment. The ESC recalled the PBAC considered that burosumab had a different safety profile compared to conventional therapy, and a claim of superior safety versus conventional therapy in the submission for XLH could not be supported (paragraph 7.8, burosumab PSD, March 2022 PBAC meeting with May 2022 Addendum).

6.22 The PBAC considered that the claim of superior comparative effectiveness was reasonable.

6.23 The PBAC considered that the claim of superior comparative safety was not adequately supported by the data. The PBAC considered that burosumab had a different safety profile compared to conventional therapy with more appreciable short-term side-effects.

Economic analysis

6.24 The submission stated that the clinical evidence was insufficient to inform an economic evaluation of burosumab for the treatment of unresectable TIO. Instead, the submission proposed listing on the basis of a 'frame of reference' approach, on the assumption that the incremental costs and benefits of burosumab compared to conventional therapy are likely similar for unresectable TIO and XLH. The submission justified the 'frame of reference' approach based on the following arguments:

- The underlying mechanisms of hypophosphataemia in TIO and XLH are the same despite different causes (i.e., tumour versus gene mutation), and lead to similar symptomatology and HRQoL;
- Burosumab works in the same way in TIO and XLH, by binding FGF23 to restore phosphate levels and improve bone mineralisation;
- The clinical and pharmacodynamic effects of burosumab among adult patients with XLH and TIO, are likely similar; and
- Based on data from the key XLH study (CL303) and unresectable TIO study (CL201) showing a slightly lower average dose for unresectable TIO, the typical treatment cost of burosumab would likely be lower for unresectable TIO, despite a higher maximum dose compared to XLH.

6.25 A 'frame of reference' approach to demonstrating cost-effectiveness was previously accepted by the PBAC at the March 2024 PBAC meeting for cabozantinib in the treatment of non-clear cell renal cell carcinoma (nccRCC), compared to the treatment of clear cell renal cell carcinoma (ccRCC). The PBAC advised that acceptance of this approach was in the context of (i) a rare subtype with limited clinical data, (ii) a small, well-defined population and (iii) relatively low financial impact (paragraph 7.9, cabozantinib PSD, March 2024 PBAC meeting).

6.26 Although unresectable TIO is a rare condition, with limited clinical data and a small, generally well-defined population, the ESC agreed with the evaluation that it was unclear whether burosumab would provide the same long-term absolute health benefits in TIO as in XLH, even with the correction of phosphate levels. The ESC noted that XLH is a lifelong genetic condition that begins in childhood, whereas TIO typically presents in adulthood. Consequently, burosumab in XLH aims to prevent or reduce long-term skeletal damage and relieve chronic symptoms, while adults with TIO have not experienced lifelong disease and have less time to accrue benefits. Therefore, despite a shared mechanism, the absolute treatment benefits of burosumab may differ between XLH and TIO at a population level. The PSCR (p3) acknowledged that

the two conditions have very different aetiologies, age of onset, and duration. However, it also noted that the frame of reference comparison presented in the submission considered only adult patients with TIO or XLH, among whom the main treatment aims of normalising serum phosphorous concentrations, correcting established skeletal damage, reducing pain and fatigue, and improving physical function and quality of life, are perhaps more comparable than those between contrasting cohorts of paediatric and adult patients with XLH. The PSCR (p3) also suggested that additional consideration could be given to the sudden onset of TIO in healthy individuals for whom the associated functional and quality of life impacts are both new and severe, compared to those with XLH who have time to adapt to these limitations.

6.27 To compare the clinical effects of burosumab in unresectable TIO and XLH, the submission presented a side-by-side unadjusted comparison of adult patients treated with burosumab in CL201 (TIO) and CL303 (XLH). Clinical data from CL303, a head-to-head RCT comparing burosumab to placebo in adults with XLH, were presented in the March 2022 burosumab submission for XLH.

6.28 The burosumab dosing regimens differed between CL201 (TIO) and CL303 (XLH), reflecting the distinct recommended doses for each indication in the product information. In CL303 (XLH), patients received a fixed dose of 1.0 mg/kg of burosumab administered Q4W, with downward dose adjustment allowed if serum phosphorus increased to > 5.0 mg/dL. In contrast, CL201 permitted upward dose titration and selected a maximum dose of 2.0 mg/kg Q2W, anticipating that doses > 1.0 mg/kg may have been needed to bring serum phosphorus levels into the LLN range in patients with TIO. Compared to subjects with XLH, FGF23 levels are higher in subjects with TIO and epidermal nevus syndrome-associated osteomalacia, and the associated hypophosphatemia is more severe.[10]

6.29 The ESC noted that there were notable differences across the baseline characteristics of patients enrolled in CL201 (TIO) and CL303 (XLH). For example, patients enrolled in CL201 (TIO) were older (57 vs 40 years), heavier (94 kg vs 71 kg), taller (167 cm vs 152 cm), had less osteoarthritis (29% vs 63%), and shorter time since diagnosis (13.7 vs 37.2 years). These differences likely reflect the distinct underlying aetiologies: XLH is a genetic condition that typically presents in childhood and may cause growth abnormalities, whereas TIO predominantly occurs in adulthood. Patients enrolled in CL201 (TIO) also had lower baseline serum phosphorus (1.60 mg/dL vs 1.98 mg/dL) and higher FGF23 levels (770 pg/mL vs 156 pg/mL), consistent with more severe FGF23-mediated hypophosphatemia in TIO. Patients enrolled in CL201 (TIO) also had more fractures (active 29% vs 12% and non-active 100% vs 59%) and pseudofractures (79% vs 47%). The PSCR (p3) acknowledged that there were notable differences in the baseline demographic and disease characteristics of patients in the respective adult TIO and XLH trials. The PSCR stated however, that the differences do not suggest there

[10] CL201 CSR, p73.

would be a major disparity between the cohorts in terms of either the likely treatment time horizon, or the timeframe over which treatment benefits might accrue.

6.30 Table 7 compares key clinical and functional outcomes reported in CL201 (TIO) and CL303 (XLH).

Table 7: Change from baseline in serum phosphorus, fracture healing, 6MWT and BPI in CL201 (TIO) and CL303 (XLH)

Outcome	CL201 (TIO)	CL303 (XLH)	
	BUR N=14[a]	BUR N=68	PBO[d] N=68
Serum phosphorus (mg/dL)			
Baseline, mean (SD)	1.60 (0.47)	2.03 (0.30)	1.92 (0.32)
Week 24, mean (SD)	2.33 (0.54)	2.53 (0.45)	2.07 (0.34)
Week 24, LS mean (SE) change from baseline	0.73 (0.12)[b]	0.39 (0.081)[c]	-0.01 (0.067)[c]
n (%) >LLN, across midpoint of dose cycles (Week 0-24)	7 (50)	63 (92.6)	5 (7.6)
mean (SD) averaged across midpoint of dose cycles (Week 0-24)	2.64 (0.76)	3.24 (0.53)	2.08 (0.30)
mean (SD) change from baseline averaged across midpoint of dose cycles (Week 0-24)	1.04 (0.56)	1.21 (0.51)	0.16 (0.272)
n (%) >LLN, across end of dose cycles (Week 0-24)	3 (21.4)	46 (67.6)	4 (6.1)
mean (SD) averaged across end of dose cycles (Week 0-24)	2.15 (0.57)	2.72 (0.45)	2.05 (0.30)
mean (SD) change from baseline averaged across end of dose cycles (Week 0-24)	0.55 (0.43)	0.69 (0.39)	0.13 (0.27)
Week 48, mean (SD)	2.53 (0.62)	2.48 (0.46)	2.47 (0.49)
Week 48, LS mean (SE) change from baseline	0.89 (0.17)[b]	0.34 (0.077)[c]	0.39 (0.078)[c]
Total active fractures and pseudofractures			
Baseline, n	249[e]	65[f]	91[f]
Week 24 grade, n (% baseline)			
Healed	3 (1.2)	28 (43.1)	7 (7.7)
Partially healed	40 (16.1)	16 (24.6)	25 (27.5)
Unchanged	186 (74.7)	9 (13.8)	41 (45.1)
Worse	1 (0.4)	2 (3.1)	11 (12.1)
New findings	19	3	0
Week 48 grade. n (% baseline)^			
Healed	18 (7.2)	41 (63.1)	32 (35.2)
Partially healed	64 (25.7)	11 (16.9)	36 (39.6)
Unchanged	151 (60.6)	6 (9.2)	11 (12.1)
Worse	7 (2.8)	0	0
New findings	17	0	1
6MWT (metres walked)			
Baseline, mean (SD)	309.0 (210.5)	356.8 (109.5)	367.4 (103.4)
Week 24, mean (SD)	334.1 (183.9)	381.5 (108.5)	369.4 (103.4)
Week 24, LS mean (SE) change from baseline	19.5 (15.6)[b]	14.8 (7.7)[c]	-5.0 (7.5)[c]
Week 48, mean (SD)	331.4 (174.7)	392.5 (107.1)	390.9 (106.5)
Week 48, mean (SE) change from baseline	25.5 (16.6)[b]	31.3 (7.3)[c]	21.4 (9.1)[c]
BPI Worst pain			
Baseline, mean (SD)	5.0 (3.2)	6.81 (1.31)	6.54 (1.43)
Week 24, mean (SD)	4.5 (3.1)	5.82 (1.92)	6.09 (2.01)
Week 24, LS mean (SE) change from baseline	-0.55 (0.69)[b]	-0.79 (0.21)[c]	-0.32 (0.22)[c]
Week 48, mean (SD)	4.1 (3.1)	5.56 (1.90)	4.91 (2.13)
Week 48, LS mean (SE) change from baseline	-0.90 (0.73)[b]	-1.05 (0.23)[c]	-1.49 (0.24)[c]
BPI Pain severity			
Baseline, mean (SD)	3.9 (2.6)	5.18 (1.53)	4.92 (1.55)
Week 24, mean (SD)	3.5 (2.6)	4.45 (1.88)	4.65 (2.13)
Week 24, LS mean (SE) change from baseline	-0.49 (0.62)[b]	-0.10 (0.21)[c]	-0.53 (0.17)[c]
Week 48, mean (SD)	3.0 (2.6)	4.19 (1.78)	3.63 (2.06)
Week 48, mean (SE) change from baseline	-0.85 (0.67)[b]	-0.79 (0.16)[c]	-1.13 (0.21)[c]

Source: Table 2-17, p44 of the submission, Tables 8 and 9, burosumab PSD March 2022, Table 11, pp131-132 of CL201 CSR.pdf, Table 24, pp140-141, Table 30, p177, Table 14.2.3.1.10, pp2518-2603, Section 10.4.2.1, p182-183 of CL303 CSR.pdf.

BPI, brief pain inventory; BUR, burosumab; ENS, epidermal nevus syndrome; GEE, generalized estimating equation; ITT, intention-to-treat; LLN, lower limit of normal; LS, least squares; PBO, placebo; PD, pharmacodynamic; SD, standard deviation; SE, standard error; TIO, tumour induced osteomalacia; XLH, X-Linked hypophosphataemia; 6MWT, 6-minute walk test.

Note: LLN was 2.5 mg/dL (0.81 mmol/L) in CL201 and CL303.

a TIO analysis set included the patients with TIO (N=14) who received at least one dose of study drug. It excluded two patients with XLH and one patient with ENS-associated osteomalacia who were in the ITT.

b In CL201, LS mean estimated using the GEE repeated measures analysis, including time as the categorical variable adjusted for baseline measurement in the model with compound symmetry covariance structure.

c In CL303, LS mean estimated from the GEE model, which includes the change from baseline or percent change from baseline measurement as the dependent variable; region, visit, treatment, actual randomization stratification and visit by treatment as fixed factors; and baseline of each measurement as a covariate, with compound symmetry covariance structure.

d All placebo patients received treatment with burosumab 1.0 mg/kg SC Q4W (after the placebo-controlled treatment period assessment at Week 24) for 24 weeks to Week 48 in the open-label treatment continuation period.

e In CL201, active fractures and pseudofractures were detected on technetium (Tc)-labelled whole body bone scan.

f In CL303, active fractures and pseudofractures identified on x-ray

6.31 Overall, the ESC noted the side-by-side comparison suggested that patients with TIO had a similar average improvement in serum phosphorus level compared to XLH, but fewer patients had serum phosphorus levels >LLN on average across the midpoint of the dose cycles between baseline to Week 24 (50% versus 92.6%). The submission suggested this may have been due to a combination of higher baseline values in the XLH cohort and the fixed dose regimen used in the CL303 study compared with the titrated regimen used for TIO in CL201. In addition, the PSCR (p2) stated the extent of benefit derived from burosumab treatment in either TIO or XLH is likely to be better defined by the degree of improvement from baseline in hypophosphataemia than the proportion of patients achieving the LLN as highlighted in published *post-hoc* analyses of burosumab XLH studies characterising the relationship between serum phosphate levels and respective fracture and patient reported outcomes (Mehta, Gosselin et al. 2024); (Mehta, Storopoli et al. 2025). The results also suggested that patients with TIO had a smaller proportion of healed and partially healed fractures and pseudofractures at Week 24 than those with XLH (1.2% versus 43.1% healed; 16.1% versus 24.6% partially healed), although patients with TIO had many more fractures at baseline. Other outcomes appeared generally similar.

6.32 To compare the average treatment cost of burosumab in unresectable TIO and XLH, the submission conducted a cost analysis for an 'average' patient weighing 80 kg over the first two years of therapy, assuming [redacted]% compliance for both populations, presented as the base case. The analysis was informed by average weight-based dosing data (mg/kg) from CL201 (unresectable TIO) and CL303 (XLH), and the effective (public hospital) price of burosumab. The base case results indicated that the cost of burosumab over the first two years of treatment was less costly for unresectable TIO ([redacted]) compared to XLH ([redacted]), due to a lower average dose for unresectable TIO (0.759 mg/kg) in CL201 than XLH (0.944 mg/kg) in CL303.

6.33 Table 8 summarises the results of the base case cost analysis as well as sensitivity analyses presented in the submission and conducted during the evaluation.

Table 8: Burosumab treatment cost comparison between unresectable TIO and XLH settings over two years (based on effective public hospital price)

	TIO cost ($)	XLH cost ($)	Difference ($)
Base case (80 kg adult, mean dose in CL201 and CL303)[a]	[redacted]	[redacted]	[redacted]
Weight			
Mean weight in CL201 (94 kg)	[redacted]	[redacted]	[redacted]
Mean weight in CL303 (71 kg)	[redacted]	[redacted]	[redacted]
Mean weight in respective studies	[redacted]	[redacted]	[redacted]
Dose			
TIO mean dosing data from CS002[b]	[redacted]	[redacted]	[redacted]
TIO mean dosing data from CN007[c]	[redacted]	[redacted]	[redacted]
TIO mean dosing data across CL201, CS002, CN007[d]	[redacted]	[redacted]	[redacted]
TIO mean dosing data across CL201, CS002, CN007 + imputation[e]	[redacted]	[redacted]	[redacted]
TIO max dose, fast titration (0.5 mg/kg increments, then Q2W)	[redacted]	[redacted]	[redacted]
TIO max dose, slow titration (0.2 mg/kg increments, then Q2W)	[redacted]	[redacted]	[redacted]
TIO min dose (no titration)	[redacted]	[redacted]	[redacted]
Max dose in CL201 and CL303	[redacted]	[redacted]	[redacted]
Min dose in CL201 and CL303	[redacted]	[redacted]	[redacted]
TIO average dose of 1 mg/kg Q4W (assumed for RSA)	[redacted]	[redacted]	[redacted]

Source: Table 3-3, p85 of the submission; Section 3 Workbook (Crysvita TIO).xlxs; Table 14.1.3.2.4, pp452-471, CL201 CSR; Table 10.6-1, p78, CS002 CSR; Table 10, p69, CN007 CSR; Table 15, p123, Table 34, p189, CL303 CSR.
Max, maximum; min, minimum; TIO, Tumour induced osteomalacia; XLH, X-Linked Hypophosphataemia.
a Corrected values to include Week 100, which the submission had incorrectly excluded.
b Carry forward last value from week 92-104 (0.96 mg/kg)
c Carry forward last value from week 48-104 (1.3 mg/kg)
d Mean of dosing data for each week, no imputation of missing data: CL201 to Week 104, CS002 to Week 88, CN007 to Week 44.
e Mean of dosing data for each week, with imputation of missing data by carrying forward the last dose to Week 104: CL201 to Week 104, CS002 to Week 88, CN007 to Week 44.

6.34 The ESC noted that the results of the sensitivity analyses illustrate the wide variation in the estimated treatment cost for TIO due to variation in the recommended dose for TIO (i.e., 0.3 mg/kg Q4W, titrated to response up to a maximum of 180 mg Q2W). Hence, the ESC considered that the main uncertainty in the submission's base case analysis was whether the average burosumab dose used in CL201 was representative of dosing likely to occur in Australian practice. Notably, no patients in CL201 were titrated to the maximum recommended dose by Week 104. In contrast, these concerns did not apply to CL303, as the recommended dosing for XLH is relatively fixed (i.e., 1 mg/kg Q4W, with limited scope for upward titration and a maximum of 90 mg Q4W). The ESC also considered that it was uncertain whether an average population weight of 80 kg was a reasonable assumption for both the TIO and XLH populations, given childhood growth abnormalities may affect adult body size in XLH, or whether the analysis should also consider the proportion of paediatric patients with TIO compared to XLH. The RSA presented in the submission assumed an average dose of 1 mg/kg Q4W for unresectable TIO (compared with approximately 0.76 mg/kg in CL201), corresponding to a higher average treatment cost for TIO.

6.35 Overall, the ESC considered that given it was unclear whether burosumab would provide the same long-term absolute health benefits in TIO as in XLH, the submission's approach of matching the price of burosumab in the two settings may not be reasonable.

Estimated PBS usage & financial implications

6.36 This submission was not considered by DUSC.

6.37 The submission used an epidemiological approach to estimate the financial impact of listing burosumab. Table 9 summarises the parameters and data sources applied in the financial analysis.

Table 9: Key inputs for financial estimates

Data	Value	Source	Comment
Eligible population			
Australian population age 1-100	Yr 1: 27,497,616 Yr 2: 27,891,971 Yr 3: 28,270,892 Yr 4: 28,634,371 Yr 5: 28,981,511 Yr 6: 29,313,131	ABS population – 3222.0 Series B. People 1-100 yrs inclusive (2026-2031) – (Prevalence)	-
Prevalence with TIO	0.698 per 100,000	Abrahamsen et. al. (2021) – population-based study in Denmark	The submission acknowledged the limited evidence base and stated that the prevalence rate could range from 0.2 to 0.9 per 100,000.
Proportion of TIO that is unresectable	25%	Estimated from "the totality of available information" (Li et al. (2020), Bosman et. al. (2022), Shan et. al. (2025), Rendina et. al. (2022), Cianferotti et. al. (2022)).	There is a wide range of reported TIO, not localised, unresectable, recurrent and persistent. Cianferotti et al. (2022) reported 54% in total, while the TGA Delegate's Overview reported approximately 35-40% of patients with TIO have tumours that cannot be localised. Rendina et. al. (2022) reported 5.5% of localised tumours were considered not surgically operable.
Uptake rate of burosumab	66.33%	The ratio of contact prevalence (defined as at least one contact per year) to total prevalence reported in Abrahamsen et. al. (2021) (0.463/0.698 = 66.33%) and assumed to remain constant across the forward estimates period.	Potential underestimate given the lack of effective alternative treatment, but under the prevalence approach adopted by the submission, uptake implicitly accounts for ongoing response, which may be less than 100%.
Compliance for burosumab	[redacted]%	Assumption	-
Treatment			
BUR dose (by weight)	1.0 mg/kg Q4W	Assumption based on experience with this recommended regimen in the clinical studies and real-world settings presented in the submission. The average dose required for adult patients across the duration of treatment is unlikely to exceed 1.0 mg/kg Q4W, with very few patients requiring a dose approaching the maximum recommended level.	The base case in the Frame of Reference calculations used dosing data from CL201, in which the mean dose across two years of therapy was 0.759 mg/kg, with all patients on Q4W dosing.
BUR scripts / patient / year	13.04	Compliance ([redacted]%) * duration (365.25/28) * 1 dose/period	The submission incorrectly assumed each patient would require one script per burosumab vial, corresponding to 3 scripts per patient per dose or 39.12 scripts per year.

Data	Value	Source	Comment
Conventional therapy dose	Phosphate: 30 mg/kg daily Calcitriol: 25 ng/kg daily	Midpoint of the recommended dosing range in Minisola et. al., 2023. Assumed an average weight of 80 kg for conventional therapy dose.	Real world use may vary widely as dose is dependent on individual response and tolerance.
Conventional therapy scripts / year	Phosphate 500mg (200 tablets): 8.77 scripts. Calcitriol 0.25 mcg (200 tablets): 14.61 scripts.	Compliance ([redacted]%) * duration (365.25 days) * doses/day (4.8 phosphate and 8 calcitriol) / pack size (200)	-
Substitution rate BUR : conventional therapy	1:1	Assumption.	The submission assumed all eligible patients initiating BUR would otherwise receive conventional therapy.
Costs			
BUR cost / script	**BUR** / **Weighted DPMQ^** **Public** 10mg $[redacted] 20mg $[redacted] 30mg $[redacted] **Private** 10mg $[redacted] 20mg $[redacted] 30mg $[redacted]	Requested effective prices are the same as the current listing of burosumab for XLH (see PBS item numbers above).	-
Conventional therapy cost / script	Oral phosphate: $152.36 Calcitriol: $46.04	Published prices (200 tablets).	-
MBS costs – burosumab administration	$20.05 per script	MBS item 3 (100%).	The unit cost was reasonable; however, as the submission incorrectly assumed one script was required per burosumab vial, it overestimated the administration costs. The submission also omitted the cost to the MBS of FGF23 testing to determine eligibility for burosumab, which would be needed once per patient.

Source: Constructed during the evaluation from pp87-89 of the submission and parameters in the Section 4 Workbook (Financial Impact).xlsx; Table 2-4, p31 of the submission; Table 14.1.3.2.4, pp452-471, CL201 CSR; TGA Delegate's Overview for burosumab (2025).
BUR, burosumab; F, female; M, male; Q4W, every 4 weeks; TIO, Tumour induced osteomalacia; XLH, X-Linked Hypophosphataemia.

^ Requested effective DPMQs public (private) for BUR 10mg: $[redacted] ($[redacted]), BUR 20mg: $[redacted] ($[redacted]), BUR 30mg: $[redacted] ($[redacted]).

6.38 Table 10 presents the estimated net financial implications to the PBS for the proposed listing of burosumab for TIO over the first six years (assumed 2026-2031) of listing. The submission excluded the RPBS co-payment from the financial estimates because it was expected to be negligible. The submission incorrectly assumed one script and one MBS service would be required for each burosumab vial dispensed, leading to an overestimation of the patient copayment and administration cost. The cost to the MBS for FGF23 testing - to determine eligibility for burosumab (item 66520 [$90 fee]), required once per patient - was also not included. The net effect of this omission on the total was likely negligible.

Table 10: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimation of number of treated patients						
TIO prevalent population	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Eligible patients with unresectable tumour	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
BUR uptake rate	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Total patients treated with BUR	[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 vials[a]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Cost to PBS of BUR ($)	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Estimation changes in use and financial impact of conventional therapy (oral phosphate and calcitriol)						
Total number of oral phosphate and calcitriol scripts	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted][2]
Phosphorus 500 mg tablets	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]
Calcitriol 0.25 mcg capsule	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]
Cost to PBS of oral phosphate and calcitriol ($)	-[redacted][4]	-[redacted][4]	-[redacted][4]	-[redacted][4]	-[redacted][4]	-[redacted][4]
Estimated financial implications for the PBS and the health budget						
Net cost to PBS ($)	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Net cost to MBS[c] ($)	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Net change to government budget ($)	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]

Source: Tables 4.1 to 4.4, pp90-91 of the submission and Section 4 Workbook (Financial Impact).xlsx.

BUR, burosumab; TIO, Tumour induced osteomalacia.

[a] In the requested restriction, prescribers must request the appropriate number of vials of the appropriate strength(s) to provide sufficient drug, based on the weight of the patient, adequate for 4 weeks, i.e. one script can have multiple vials and so the number of scripts would be lower than the number of vials.

The redacted values correspond to the following ranges:

[1] < 500

[2] 500 to < 5,000

[3] $0 to < $10 million

[4] net cost saving

6.39 The total cost to the PBS of listing burosumab was estimated to be $10 million to < $20 million over the first 6 years of listing. The ESC noted the estimates will likely be higher if patients without normalised serum phosphate levels are allowed to continue treatment with burosumab; however, the degree of this increase was uncertain. The ESC noted that the financial estimates were also uncertain given the lack of epidemiological data on which to derive the eligible population and the expected utilisation of burosumab for unresectable TIO in Australia. On balance, the ESC considered that the proposed estimates may reflect a reasonable estimate for the purposes of a RSA.

Financial Management – Risk Sharing Arrangements

6.40 The sponsor proposed expanding the existing RSA for XLH to include patients with unresectable TIO. The existing RSA consists of a [redacted]% rebate for any expenditure over the agreed expenditure caps. The sponsor stated that they will only be able to proceed with the new listing if the current financial caps are increased in line with the expected population of patients with unresectable TIO.

6.41 The ESC considered that a combined RSA for the TIO and XLH populations was reasonable, noting that it would manage potential continued use of burosumab in patients whose serum phosphate levels had not returned to normal after 6 months of treatment.

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

7 PBAC Outcome

7.1 The PBAC recommended burosumab for the treatment of unresectable tumour induced osteomalacia (TIO) characterised by fibroblast growth factor 23 (FGF23) mediated hypophosphataemia due to tumours that cannot be curatively resected or localised. The PBAC noted that the evidence was limited but considered that burosumab was likely superior compared to conventional therapy (which consists of oral phosphorus and calcitriol) at normalising phosphate levels and has a different, but non-inferior, safety profile. The PBAC accepted the submission's assumption that the incremental costs and benefits of burosumab compared to conventional therapy are likely similar for adult patients with unresectable TIO and X-linked hypophosphataemia (XLH, currently PBS-listed indication for burosumab) and recommended listing at the same price per vial. The PBAC considered that the estimated financial impact was reasonable and advised that the proposed risk sharing arrangement (RSA) was adequate to manage uncertainties relating to the duration of treatment and the long-term absolute health benefits of burosumab and the potential for use in patients who did not obtain a normal serum phosphate level after 6 months of treatment.

7.2 The PBAC, noting that current therapies such as oral phosphorus and calcitriol result in side effects and are not effective for some patients, considered that there was a high unmet clinical need for new treatments for TIO. The PBAC acknowledged the sponsor hearing and the input received from an organisation that supported the submission and described the benefits of treatment on physical function and quality of life.

7.3 The PBAC considered the clinical place for burosumab is as an alternative option to conventional therapy when surgical treatment is not possible or is ineffective. The PBAC accepted the submission's nominated main comparator, conventional therapy, including oral phosphorus (1 to 3 g per day, divided into 4 to 6 daily doses) and oral calcitriol (0.5 to 1.5 mcg per day, divided into 2 to 3 daily doses). The PBAC noted that conventional therapy is a historical treatment regimen informed mainly by convention and experience rather than clinical data.

7.4 The PBAC noted the the submission was based on three small single-arm non-comparative studies of burosumab in adults with unresectable TIO (CL201, CS002 and CN007). While efficacy outcomes including the assessment of biochemical pharmacodynamic (PD) parameters (serum phosphorus) or bone health measurements (bone biopsy histomorphometry, 99mTc bone scans, DXA and radiographs) were objective, other patient reported outcomes (pain, fatigue or

physical function) or adverse events (AEs) were subjective and may be affected by reporting bias.

7.5 The PBAC considered the clinical claim of superior effectiveness was likely reasonable, despite the absence of comparative evidence versus conventional therapy, as well as substantial uncertainties and evidence gaps (e.g., no clinical data in paediatric patients). The three single-arm studies presented in the submission found that, on average, adults treated with burosumab showed significant improvements from baseline in serum phosphate levels and other outcomes by Week 24, and that these improvements were maintained up to Week 144. The PBAC noted the additional evidence in the submission from real-world studies with burosumab, conventional therapy and surgical treatments for TIO was broadly consistent with the results from the main clinical studies presented in the submission. Although the relative effectiveness versus conventional therapy for unresectable TIO was unknown, the PBAC recalled it had previously accepted that burosumab was superior to conventional therapy for XLH in both paediatric and adult patients based on head-to-head evidence (paragraphs 6.38 and 6.41, burosumab PSD, March 2022 PBAC meeting with May 2022 Addendum).

7.6 The PBAC considered that the claim of superior comparative safety over conventional therapy was uncertain as there were limited comparative data available. The PBAC recalled that based on the comparative evidence presented in the submission for XLH, the PBAC previously considered that burosumab had more appreciable short-term side-effects such as dental caries, tooth abscesses, diarrhoea, cough and administration site reactions, whereas long-term use of conventional therapy was associated with nephroacalcinosis and secondary hyperparathyroidism. Additionally, the PBAC noted the TGA approved Product Information was updated to include hypersensitivity reactions (rash, drug eruption and hypersensitivity) and restless leg syndrome as selected adverse events in adults with TIO. Therefore, consistent with its recommendation for XLH and based on the evidence available, the PBAC considered that burosumab had a different safety profile compared to conventional therapy with more appreciable short-term side-effects.

7.7 The submission proposed listing on the basis of a 'frame of reference' approach, on the assumption that the incremental costs and benefits of burosumab compared to conventional therapy are likely similar for unresectable TIO and XLH, stating that the clinical evidence was insufficient to inform an economic evaluation of burosumab for the treatment of unresectable TIO. The PBAC noted that in terms of benefits, the side-by-side comparison (see Table 7) suggested that adult patients with TIO had a similar average improvement in serum phosphate level compared to those with XLH and that most other outcomes appeared generally similar. The PBAC acknowledged that there were differences in the diseases, i.e., XLH is a lifelong genetic condition that begins in childhood whereas TIO typically presents in adulthood, but overall, considered that for adult patients the functional and quality of life impacts would be comparable for both patient groups.

7.8 To compare the average treatment cost of burosumab in unresectable TIO and XLH, the PBAC noted that the submission conducted a cost analysis for an 'average' patient weighing 80 kg over the first two years of therapy, assuming 100% compliance for both populations. The PBAC noted the base case results indicated that the cost of burosumab over the first two years of treatment was less costly for unresectable TIO ($[redacted]; average dose = 0.759 mg/kg) compared to XLH ($[redacted]; average dose = 0.944 mg/kg). The PBAC noted that the results of the sensitivity analyses illustrated the wide variation in the estimated treatment cost for TIO due to variation in the recommended dose (i.e., 0.3 mg/kg Q4W, titrated to response up to a maximum of 180 mg Q2W; see Table 8) and considered that the main uncertainty in the submission's base case analysis was whether the average burosumab dose used in CL201 was representative of dosing likely to occur in Australian practice. The PBAC noted the pre-PBAC response stated that on balance, the sponsor believed it was likely that burosumab would provide at least the same degree of patient relevant clinical benefit to adults with TIO as compared to those with XLH, and that this will probably be at a lower total treatment cost, but it accepted that the supportive evidence here is scarce and weak.

7.9 The PBAC reflected on previous determinations where a frame of reference approach was used to make a decision. The PBAC compared the available evidence, nature of the benefits, numbers of patients expected to be treated, and the cost per patient over two years for patients with TIO and XLH treated with burosumab. The PBAC considered that, although some uncertainty in dosing remained, in the context of this rare disease, burosumab would be considered acceptably cost-effective at a cost of not more than what is currently paid for XLH.

7.10 The PBAC noted the submission used an epidemiological approach to estimate the financial impact of listing burosumab. The PBAC noted there were uncertainties given the lack of epidemiological data from which to derive the eligible population and the expected utilisation. The PBAC also noted that the assumed average dose of burosumab in the financial estimates was 1 mg/kg every four weeks as compared with 0.76 mg/kg in the frame of reference approach. Further, the PBAC acknowledged that patients without normalised serum phosphate levels who are allowed to continue treatment with burosumab may increase the financial estimates but considered that the degree of this increase was unknown. However, on balance, the PBAC considered the submission's estimated patient numbers, the conservative uptake rate of 66.33% and resulting financial impact were reasonable

7.11 The PBAC noted a Deed of Agreement exists between the sponsor and the Commonwealth for burosumab in XLH with a [redacted]% rebate for any expenditure on burosumab over the agreed expenditure caps. The PBAC agreed that the proposal presented in the submission to expand the existing RSA for XLH to include patients with unresectable TIO was reasonable. The PBAC noted that there were uncertainties related to the magnitude of clinical effectiveness, duration of treatment, potential continued use of burosumab in patients whose serum phosphate levels had not returned to normal after 6 months of treatment and the variable weight-based daily

dosing, but considered these uncertainties would be adequately managed through the RSA.

7.12 In terms of the restriction, the PBAC advised that burosumab should be listed as a Section 100 – Highly Specialised Drugs Program with an Authority Required (telephone/electronic), complex authority required listing to be consistent with the current PBS listing for XLH. The PBAC considered that the changes suggested by the Secretariat were appropriate and agreed that for continuing treatment beyond 24 weeks, the restrictions should allow patients who achieve clinical benefit to continue treatment without strict normalisation of phosphate levels. The PBAC considered that the addition of a clinical to the continuing and grandfather restrictions stating that the 'Patient must have achieved normalisation in serum phosphate levels or, the condition must have been reviewed by a second specialist physician with expertise in the management of this condition, confirming that continuing therapy is clinically required' was reasonable. For consistency, the PBAC also advised that this change should flow on to the restrictions for XLH.

7.13 The PBAC agreed with the submission that genetic testing would not be required to rule of hereditary causes of FGF23 related hypophosphataemia, but considered that the initial supply restriction should contain wording that encourages prescribers to rule out other non-hereditary forms of the condition such as Fanconi syndrome, iron-infusion associated hypophosphataemia or post renal transplantation hypophosphataemia prior to initiation of burosumab.

7.14 The PBAC accepted a grandfather clause to allow patients receiving compassionate access to initiate PBS-funded burosumab. The PBAC advised applying a standard 12-month expiry along with the relevant clinical criteria as included in the recommended listing section.

7.15 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*.

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

7.17 The PBAC recommended that the Early Supply Rule should not apply noting that it currently does not apply to XLH PBS listings.

7.18 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* 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.

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

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Initial, continuing & grandfather

MEDICINAL PRODUCT medicinal product pack		PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
BUROSUMAB						
burosumab 10 mg/mL injection, 1 mL vial		NEW (Public) NEW (Private)	1	1	5	Crysvita
burosumab 20 mg/mL injection, 1 mL vial		NEW (Public) NEW (Private)	1	1	5	
burosumab 30 mg/mL injection, 1 mL vial		NEW (Public) NEW (Private)	1	1	5	
Concept ID	**Category / Program:** ☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)					
	Prescriber type: ☒ Medical Practitioners					
	Benefit type: ☒ Authority Required (Telephone/Online PBS Authorities System)					
	Authority type: ☒ Complex Authority Required (CAR)					
	Prescribing rule level:					
	Administrative Advice: No increase in the maximum number of repeats may be authorised.					
	Administrative Advice: Special Pricing Arrangements apply.					
	Administrative Advice: 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. Monday to Friday).					
	Indication: Tumour-induced osteomalacia					
	Treatment Phase: Initial treatment – new patient					
	Clinical criteria:					
	Patient must have a confirmed diagnosis of hypophosphataemia in tumour induced osteomalacia demonstrated by the presence of all of the following: (i) chronic clinical symptoms of fatigue, bone pain, muscle weakness and/or (pseudo) fractures; (ii) elevated (or inappropriately normal) serum or plasma FGF-23 levels above the mean of the assay-specific reference range (iii) a serum phosphate concentration below the age adjusted lower limit of normal; (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 not be a candidate for curative surgical resection as a result of either: (i) inability to locate the causative tumour using all available functional imaging technologies; (ii) inability to completely resect the causative tumour due to size, anatomical location, or other patient contraindications or comorbidities; OR
	Patient must have demonstrated persistent hypophosphatemia despite complete surgical resection of the suspected causative tumour.
	Treatment criteria:
	Must be treated by a medical practitioner identifying as at least one of the following specialists: (i) paediatric endocrinologist, (ii) paediatric nephrologist, (iii) endocrinologist, (iv) nephrologist.
	Prescribing instructions: 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 4 weeks, according to the specified dosage in the approved Product Information (PI). A separate authority prescription form must be completed for each strength requested. Up to a maximum of 5 repeats will be authorised.
	Prescribing instructions: Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.
	Prescribing instructions: Prescribers should, where possible, rule out all other non-hereditary forms of FGF23 related hypophosphataemia such as Fanconi syndrome, iron-infusion associated hypophosphataemia or post renal transplantation hypophosphataemia, prior to initiating patients on burosumab treatment for this condition.
	Indication: Tumour-induced osteomalacia
	Treatment Phase: Continuing treatment
	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; OR
	The condition must have been reviewed by a second specialist physician with expertise in the management of this condition, confirming that continuing therapy is clinically required.
	Treatment criteria:
	Must be treated by a medical practitioner identifying as at least one of the following specialists: (i) paediatric endocrinologist, (ii) paediatric nephrologist, (iii) endocrinologist, (iv) nephrologist.
	Prescribing instructions: 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 4 weeks, according to the specified dosage in the approved Product Information (PI). A separate authority prescription form must be completed for each strength requested. Up to a maximum of 5 repeats will be authorised.
	Prescribing instructions: Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.
	Indication: Tumour-induced osteomalacia
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply – 'Grandfather' arrangements
	Clinical criteria:

	Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to [date of listing].
	AND
	Clinical criteria:
	Patient must have, prior to initiating treatment with this drug, a confirmed diagnosis of hypophosphataemia in tumour induced osteomalacia demonstrated by the presence of all of the following: (i) chronic clinical symptoms of fatigue, bone pain, muscle weakness and/or (pseudo) fractures; (ii) elevated (or inappropriately normal) serum or plasma FGF-23 levels above the mean of the assay-specific reference range (iii) a serum phosphate concentration below the age adjusted lower limit of normal; (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 not have been a candidate for curative surgical resection, prior to initiating treatment with this drug, as a result of either: (i) inability to locate the causative tumour using all available functional imaging technologies; (ii) inability to completely resect the causative tumour due to size, anatomical location, or other patient contraindications or comorbidities; OR
	Patient must have had demonstrated persistent hypophosphatemia despite complete surgical resection of the suspected causative tumour prior to initiating treatment with this drug
	AND
	Clinical criteria:
	Patient must have achieved normalisation in serum phosphate levels; OR
	The condition must have been reviewed by a second specialist physician with expertise in the management of this condition, confirming that continuing therapy is clinically required.
	Treatment criteria:
	Must be treated by a medical practitioner identifying as at least one of the following specialists: (i) paediatric endocrinologist, (ii) paediatric nephrologist, (iii) endocrinologist, (iv) nephrologist.
	Prescribing instructions: 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 4 weeks, according to the specified dosage in the approved Product Information (PI). A separate authority prescription form must be completed for each strength requested. Up to a maximum of 5 repeats will be authorised.
	Prescribing instructions: Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.
	Prescribing Instructions: A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
	Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

Flow on changes

8.2 Flow- on changes to the continuing treatment phase of burosumab PBS listings (item codes 13140N, 13163T, 13136J, 13145W, 13154H, 13155J) for X-linked hypophosphataemia for consistency with recommended listing for TIO:

	Clinical criteria:
	Patient must have achieved normalisation in serum phosphate levels*; OR*
	The condition must have been reviewed by a second specialist physician with expertise in the management of this condition, confirming that continuing therapy is clinically required.

	~~**Prescribing Instructions:**~~ ~~Where adequate response to treatment with this drug cannot be demonstrated, the treating physician must confirm that continuing therapy has been determined to be clinically required by a second specialist physician with expertise in the treatment of X-linked hypophosphataemia.~~

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

9 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.

10 Sponsor's Comment

The sponsor had no comment.