Medical Services Advisory Committee (MSAC) Public Summary Document

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)

Applicant: **Department of Health and Aged Care on behalf of the Hypophosphatemic Working Party of the Australian and New Zealand Bone and Mineral Society**

Date of MSAC consideration: **1 – 2 August 2024**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of 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) has been submitted by the Department of Health and Aged Care (the department) on behalf of the Hypophosphatemic Working Party of the Australian and New Zealand Bone and Mineral Society (ANZBMS).

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported the creation of a new MBS item (below) for FGF-23 testing to determine eligibility for burosumab on the PBS in patients with a high pre-test probability of X-linked hypophosphatemia (XLH). MSAC considered that there was a clear clinical need for this test as it was required to determine eligibility for a PBS-listed therapy (burosomab), the test would be used by a small patient cohort and the financial impact of the test was low.

MSAC noted the late request from the applicant to broaden the scope of the test to include FGF-23 testing for the diagnosis of all types of FGF-23 dependent hypophosphatemia (beyond the diagnosis of XLH alone). MSAC requested that the need for assessment of this request should be weighed against the resources required and proposed that the Department of Health and Aged Care seek MSAC Executive advice on a suitable pathway for consideration of this request.

Category 6 – Pathology Services	Group P2 – Chemical (to be confirmed)
MBS item XXXXX Fibroblast growth factor 23 quantification in serum or plasma, requested by a specialist or consultant physician to determine eligibility for a relevant treatment listed on the Pharmaceutical Benefits Schedule Fee: $90.00 Benefit: 75% = $67.50 85% = $76.50	

Consumer summary

This is an application from the Australian Government Department of Health and Aged Care, on behalf of the Hypophosphatemic Working Party of the Australian and New Zealand Bone and Mineral Society (ANZBMS), requesting Medicare Benefits Schedule (MBS) listing of fibroblast growth factor 23 (FGF-23) testing for people with a high probability of X-linked hypophosphatemia (XLH).

XLH is a rare inherited condition that affects a number of body systems, including the bones. People with XLH have abnormally high levels of the hormone FGF-23 in their bodies. High FGF-23 levels lead to low levels of a mineral called phosphate. Phosphate is one of the minerals, along with calcium, that is stored in bones and used to build and keep them strong. Bone is a living, active tissue. It has its own specialised cells that work continuously to replace old bone tissue with new bone tissue over the whole lifecycle. Bone tissue is made of protein and collagen, which provides a framework for minerals that get laid down in the framework as tiny microcrystals. The minerals make bones hard and the collagen provides flexibility for the bone to resist breaking under tension.

When there is not enough phosphate in the body, like in people with XLH, the bones can't mineralise properly, so they grow to be malformed, painful and break easily. People with this condition, called rickets, osteomalacia, or 'soft bone disease', can have chronic pain and significant problems with muscle and joint function, limiting their mobility.

The diagnosis of XLH includes a number of steps, one of which is testing for high FGF-23 levels (or unusually normal FGF-23 levels in people who have other symptoms of XLH). People who have a diagnosis of XLH including high or unusually normal FGF-23 levels are eligible to access burosumab, a medication for the treatment of XLH, on the Pharmaceutical Benefits Scheme (PBS).

The proposed test to look for levels of FGF-23 is a simple blood test. People found to have high levels of FGF-23 and who are diagnosed with XLH can access burosumab, a medication that binds to and inactivates FGF-23. Treatment with burosumab is not a cure, but it increases phosphate levels which improves bone mineralisation and reduces the severity of rickets in people who have XLH.

Burosumab has been available on the PBS for 2 years and people are currently accessing it through a genetic test that isn't perfect at detecting whether someone has the gene that causes XLH. Also, the genetic test is not available in all parts of Australia.

MSAC noted that the budget impact of the proposed test will be very small, because the test is low cost and there are not many people suspected to have this condition (about 300 people in Australia). Once people are tested and diagnosed, the annual cost to the MBS will be even smaller because there won't be many new cases each year.

The ANZBMS, on behalf of which the application was made, also requested during the assessment process that the testing be expanded to all people suspected of having high FGF-23 levels resulting in low phosphate, not just those with suspected XLH. However, this request came too late for MSAC to consider at their August 2024 meeting and evidence for these extra populations had not been provided for MSAC to consider. MSAC referred consideration of funding for the proposed broader population to the Department of Health and Aged Care (the department), and requested the department seek MSAC Executive advice on the most suitable way to consider this request.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC supported listing FGF-23 testing for people with X-linked hypophosphatemia to access burosumab. MSAC considered the test to be safe and effective, and that it would have a very small impact on the MBS budget.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this application submitted by the department on behalf of the Hypophosphatemic Working Party of the Australian and New Zealand Bone and Mineral Society (ANZBMS) is for MBS listing of FGF-23 testing for patients with a high pre-test probability of XLH to determine eligibility for burosumab on the PBS.

In December 2023, the MSAC Executive advised that an assessment focused on the financial implications of FGF-23 testing for burosumab access should be prepared for MSAC consideration. Given the population was defined by the co-dependency with the PBS eligibility criteria for burosumab, and the anticipated small population size and budget impact, the MSAC Executive advised that the focused assessment could proceed directly to MSAC, bypassing PASC and ESC.

MSAC noted the late request by the ANZBMS to expand testing to include additional populations, that is, FGF-23 testing for the diagnosis of all types of FGF-23–dependent hypophosphatemia (beyond the diagnosis of XLH alone). This would extend testing to patients suspected of having other FGF-23 disorders that, while not eligible for burosumab treatment, might benefit from precise diagnosis of the disorder. MSAC noted that the ANZBMS advised that, although the diagnostic pathway is similar, there are a small number of diagnoses in addition to XLH that also have high levels of FGF-23 as a cause for hypophosphatemia, such as tumour-induced hypophosphatemia, autosomal dominant and autosomal recessive hypophosphatemic rickets, fibrous dysplasia/McCune–Albright syndrome, iron infusion-associated hypophosphatemia and post-renal transplantation. However, MSAC noted that the request was too late to be assessed and that evidence for these additional populations was not included within the current application and assessment. Therefore, MSAC referred consideration of funding for the proposed broader population to the department, and requested the department seek MSAC Executive advice on the most suitable way to consider this request.

MSAC noted that burosumab has been available on the PBS for 2 years and patients have been accessing burosumab through renal disorder genetic testing for *PHEX* pathogenic variants. A new, specific MBS item for FGF-23 testing for XLH diagnosis to access burosumab would be more appropriate, as *PHEX* testing only captures about 80% of people with XLH.

MSAC noted the proposal to exclude patients from FGF-23 testing if they already have a documented confirmation of a *PHEX* pathogenic variant. The department advised that it would not be possible to monitor if *PHEX* testing had been previously conducted, as these MBS items are not exclusively for *PHEX* variant testing and some patients move in and out of the public and private testing space. Thus, MSAC concluded that it would be impractical to impose any restriction preventing patients who have already accessed *PHEX* testing from accessing FGF-23 testing, but this may be included as an Explanatory Note.

MSAC noted the public consultation feedback from three organisations: Australian Pathology, Public Pathology Australia and ANZBMS. Feedback from Australian Pathology and Public Pathology Australia focussed on pathology considerations including the proposed MBS fee. Feedback from ANZBMS was supportive, including that burosumab treatment leads to significant improvements in quality of life (stiffness, muscle and bone pain and physical function). MBS funding of the FGF-23 test will particularly benefit patients in lower socioeconomic groups by helping them to arrive at a diagnosis of XLH which will enable them to access treatment, thus ensuring equity of access. ANZBMS also stated that the test would rapidly rule out patients with non-FGF-23 causes of kidney phosphate wasting who would otherwise require more expensive diagnostic services such as gallium-Dotatate PET imaging. Finally, MSAC noted that the ANZBMS stated that FGF-23 testing would enable testing of family members of patients with confirmed

XLH who also demonstrate reduced phosphate, leading to a more accurate recognition of this disorder.

MSAC noted the proposed MBS descriptor and fee, and that the MSAC Executive had suggested a more detailed item descriptor aligning with the PBS listing for burosumab. However, MSAC noted that the increased complexity added to the MBS item by repeating the PBS requirements increases the risk that patients will have to pay out-of-pocket for FGF-23 testing as pathology laboratories would have difficulty ascertaining whether patients met the PBS requirements and if they could not be certain, would be required to bill the patient privately. MSAC therefore supported the simplified MBS descriptor as proposed by the department.

MSAC noted feedback regarding the proposed fee ($90). Public Pathology Australia and the ANZBMS Clinical Practice and Therapeutics Committees were both supportive of the fee, whereas Australian Pathology was not. Australian Pathology cited that one laboratory's fee for the service was $111.10 and that additional costs are also associated with collecting, freezing and transporting the sample to the reference laboratory. However, MSAC advised that these additional costs were available for rebate under other MBS items, and it was not appropriate to include them in the testing fee. Therefore, MSAC considered the fee of $90 to be appropriate.

MSAC agreed with the proposed population in the Department-contracted assessment report (DCAR), which was patients with a high pre-test probability of XLH rickets to establish a diagnosis or disease (sub)classification in symptomatic or affected patients with suspected XLH. Such patients would be identified by elevated (or inappropriately normal) serum or plasma FGF-23 levels, in conjunction with other diagnostic findings, to determine eligibility for treatment with burosumab. MSAC noted that recommendations from clinical guidelines and consensus statements vary and do not always include FGF-23 testing as part of the essential testing for a diagnosis of XLH, but that testing is required to access PBS listed burosumab. MSAC also considered the comparator of no testing and no access to burosumab to be appropriate but noted that genetic testing for a *PHEX* pathogenic variant to gain access to burosumab could be considered a comparator to FGF-23 testing.

MSAC noted that the current application did not include an economic evaluation, and that instead, a total budget impact approach was taken. The total budget impact of FGF-23 testing for patients with a high pre-test probability of XLH to the MBS was $3,366 in Year 1, decreasing to $765 in Year 6.

4. Background

The Medical Services Advisory Committee (MSAC) has not previously considered FGF-23 testing for determining eligibility for burosumab on the PBS.

Burosumab was listed on the PBS on 1 November 2022 for the treatment of XLH. The Pharmaceutical Benefits Advisory Committee (PBAC) application history for burosumab is summarised in Table 1.

To access burosumab on the PBS a patient must meet the following clinical criteria:

- have a documented confirmation of phosphate-regulating endopeptidase homolog X-linked (PHEX) pathogenic variant; OR
- have a confirmed diagnosis of XLH demonstrated by the presence of all of the following:
    (i) a serum phosphate concentration below the age adjusted lower limit of normal

(ii) current or historical (for those with growth plate fusion) radiographic X-ray evidence of rickets

(iii) elevated (or inappropriately normal) serum or plasma FGF-23 levels of above the mean of the assay-specific reference range

(iv) renal phosphate wasting demonstrated by a ratio of tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) according to age specific normal ranges using the second morning urine void and paired serum sample measuring phosphate and creatinine.

Item (iii) under the second bullet point is the subject of this application.

The co-dependency of the FGF-23 test and burosumab was not identified during the PBAC process, and FGF-23 testing is not currently funded on the MBS. To access burosumab on the PBS, the cost of FGF-23 testing is currently borne by the patient or the hospital. All other tests required to confirm a diagnosis of XLH for the purpose of accessing burosumab on the PBS are funded on the MBS.

In October 2023, the Hypophosphatemic Working Party of the ANZBMS sought advice from the department on how to request a new MBS item for the analysis of plasma or serum FGF-23 in patients with a high pre-test probability of XLH who otherwise may have to pay privately for the test in order to gain access to burosumab treatment on the PBS. The PBAC Executive referred the matter to the MSAC Executive with advice that MBS funding for FGF-23 testing should be pursued, and the current PBS eligibility criteria should be retained. The MSAC Executive advised that a brief assessment report focused on the financial implications of FGF-23 testing should be developed for MSAC consideration and could proceed on the direct pathway to MSAC, bypassing the PICO Advisory Sub-committee (PASC) and the Evaluation Sub-committee (ESC).

Table 1 PBAC application history for burosumab

PBAC meeting	Application details Population	Key points
March 2021	BUROSUMAB, Injection 10 mg in 1 mL, Injection 20 mg in 1 mL, Injection 30 mg in 1 mL Kyowa Kirin Australia Pty Ltd® Paediatric patients (< 18 years) with a confirmed diagnosis of XLH	Outcome: Rejected • The PBAC considered that there were complex issues relating to the clinical evidence presented and the proposed restriction. In addition, the PBAC considered that the ICER was high and likely underestimated and that the financial estimates were highly uncertain. • The PBAC noted that the proposed restriction only required patients to have 'confirmed XLH in the patient's medical records'. The PBAC recommended that the restriction include more clinically based criteria such as serum phosphate levels and radiographic evidence of rickets and include confirmation of a PHEX pathogenic variant. • The PBAC recommended that any future submission should present all the available clinical data for burosumab use in children and in adults. • The PBAC advised that a resubmission, which proposed revised restrictions, presented all available clinical data, included a substantial price reduction and a revised economic evaluation, presented updated utilisation and financial impact estimates, and which presented a proposed RSA for the age agnostic XLH population, could be lodged using the standard re-entry pathway.
March 2022	BUROSUMAB, Injection 10 mg in 1 mL, Injection 20 mg in 1 mL, Injection 30 mg in 1 mL	Outcome: Not recommended • The resubmission included an age agnostic requested listing. • The requested restriction regarding clinically defined initiation criteria was amended to reflect outcomes of a PBAC-convened clinical expert

PBAC meeting	Application details Population	Key points
	Kyowa Kirin Australia Pty Ltd® Patients with a diagnosis of XLH confirmed by specified genetic and/or clinical/laboratory criteria	consultation meeting held in May 2021. This wording is consistent with the approved listing and includes FGF-23 testing. • The PBAC considered that the ICER was unacceptably high at the proposed price and that an RSA was needed to address substantial uncertainties around the financial estimates, including the impact associated with use of higher doses. • The PBAC considered the outstanding issues could be resolved in a simple resubmission for burosumab and that an early resolution pathway would be acceptable. It was noted that the following changes may address the outstanding issues without requiring further re-evaluation: ○ a further price reduction which results in ICERs of approximately $255,000 to < $355,000 per QALY for both the paediatric and adult populations; and ○ a revised RSA which offers a rebate of 100% for use over the financial impact estimates.
May 2022	BUROSUMAB, Injection 10 mg in 1 mL, Injection 20 mg in 1 mL, Injection 30 mg in 1 mL Kyowa Kirin Australia Pty Ltd® Patients with a diagnosis of XLH confirmed by specified genetic and/or clinical/laboratory criteria	Outcome: Recommended • The PBAC recommended the listing of burosumab for the treatment of patients with XLH. The PBAC noted the high clinical need and previous strong consumer support for treatments for this condition. The PBAC considered that the ICERs for both the paediatric and adult populations were acceptable at the proposed price and that the proposed RSA was adequate to manage the risks associated with the uncertainties relating to the estimated financial impact to the PBS. • No changes were made to the requested restriction in regard to clinically defined initiation criteria in this resubmission.

FGF-23 = fibroblast growth factor 23; ICER = incremental cost effectiveness ratio; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PHEX = phosphate-regulating endopeptidase homolog X-linked; QALY = quality adjusted life year; RSA = Risk Sharing Arrangement; XLH = X-linked hypophosphatemia.
Source: PBAC Public Summary Documents for the relevant applications.

Request to expand application

During the preparation of the assessment report the Hypophosphatemic Working Party made an additional request to expand the scope of the application to include FGF-23 testing for the diagnosis of all types of FGF-23 dependent hypophosphatemia (beyond the diagnosis of X-linked hypophosphatemia alone). This would include tumour induced hypophosphatemia, autosomal dominant and autosomal recessive hypophosphatemic rickets, fibrous dysplasia/McCune-Albright syndrome, iron infusion-associated hypophosphatemia, and post renal transplantation hypophosphatemia.

The proposal included both an expansion of the population (from patients with a high pre-test probability of XLH to patients who may have any type of FGF-23 dependent hypophosphatemia), as well as a change to the indication for testing (from only assessing eligibility for burosumab on the PBS to also including the diagnosis of all types of FGF-23 dependent hypophosphatemia). This request was beyond the scope of the current brief assessment that was requested by the MSAC Executive specifically for FGF-23 testing to confirm the diagnosis of XLH for the purpose of accessing burosumab on the PBS.

Estimation of the utilisation and financial impact of the expansion of FGF-23 testing to include the diagnosis of any type of FGF-23 dependent hypophosphatemia would require consideration of the position of the test within the diagnostic pathway for children and adults in the Australian setting, and assessment of the clinical utility of FGF-23 testing in these expanded populations.

5. Prerequisites to implementation of any funding advice

FGF-23 testing is already being performed in Australia by select laboratories. As is the case for other pathology tests, FGF-23 testing involves in-vitro diagnostic medical devices (IVDs) that require approval by the Therapeutic Goods Administration (TGA) and inclusion on the Australian Register of Therapeutic Goods (ARTG), or in house IVDs developed by the laboratories that are accredited by the National Association of Testing Authorities (NATA) and notified to the TGA.

It is noted that NSW Health Pathology (Royal North Shore Hospital Laboratory), Alfred Pathology Service (Alfred Hospital), and Pathology Queensland Central Laboratory are currently NATA accredited to perform FGF-23 testing and appear to be the only laboratories in Australia performing the test.

6. Proposal for public funding

A new MBS item has been proposed for FGF-23 testing to determine eligibility for burosumab on the PBS.

XLH is caused by a mutation in the PHEX gene, leading to elevated FGF-23 levels and consequent hypophosphatemia due to increased phosphaturia and suppression of 1,25-dihydroxyvitamin D synthesis. Low phosphate levels result in under-mineralisation of the skeleton, a condition called rickets or osteomalacia. Burosumab, a monoclonal antibody, binds to FGF-23 and reduces its action on the kidney to excrete phosphate, thus increasing serum phosphate and allowing bone mineralisation to return to normal.

Intact FGF-23 (iFGF-23) levels are reported to be 'inappropriately normal' or elevated in 74.2% to 100% of patients with XLH.[1]

Worldwide, there is variation amongst FGF-23 assays in the type of FGF-23 detected (iFGF-23, or both intact and C-terminal FGF-23), whether the testing can be performed on plasma or serum, the sample volume required, units of measurement, and reference ranges. The three laboratories conducting FGF-23 testing in Australia use the same immunoassay (Diasorin Liaison) – which detects iFGF23 – and apply the same reference interval.

FGF-23 levels can also be influenced by phosphate and vitamin D therapy and are most informative in untreated patients.[2] For this reason, the 2022 'Interdisciplinary management of FGF23-related phosphate wasting syndromes: a consensus statement on the evaluation, diagnosis and care of patients with X-linked hypophosphataemia' suggests that for initial

[1] Munns CF, Yoo HW, Jalaludin MY, Vasanwala R, Chandran M, Rhee Y, BUT WM, Kong APK, Su PH, Numbenjapon N, Namba N, Imanishi Y, Clifton Bligh RJ, Luo X, Xia W (2023) 'Asia Pacific consensus recommendations on X linked hypophosphatemia: diagnosis, multidisciplinary management, and transition from pediatric to adult care', JBMR Plus, 7(6):e10744, doi:10.1002/jbm4.10744.

[2] Haffner D, Emma F, Eastwood DM, Biosse Duplan M, Bacchetta J, Schnabel D, Wicart P, Bockenhauer D, Santos F, Levtchenko E, Harvengt P, Kirchhoff M, Di Rocco F, Chaussain C, Brandi ML, Savendahl L, Briot K, Kamenicky P, Rejnmark L, Linglart A (2019) 'Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia', Nat Rev Nephrol, 15:435–455, doi:10.1038/s41581-019-0152-5.

diagnostic purposes, FGF-23 plasma samples be collected one to two weeks after phosphate and calcitriol (active form of Vitamin D) discontinuation if the patient is already receiving treatment.[3]

The 2023 'Asia-Pacific consensus recommendations on X-linked hypophosphatemia' recognises these limitations, advising that 'results should be interpreted with caution because of lack of standardization and potential influence by treatment'.[1]

Proposed descriptor

The MBS item proposed by the department for consideration by the MSAC Executive is presented in Table 2. The proposed item reflected the department's preference for simplified wording without reproduction of the clinical criteria from the PBS restriction for burosumab.

Table 2 MBS item proposed by the department for FGF-23 testing to determine eligibility for burosumab on the PBS

Category 6 – Pathology Services Group P2 – Chemical (to be confirmed)
MBS item number XXXXX Fibroblast growth factor 23, quantification in serum or plasma for the diagnosis of hypophosphatemia if: a) the service is requested by a specialist or consultant physician To determine eligibility for a treatment listed on the Pharmaceutical Benefits Schedule Fee: to be confirmed

FGF-23 = fibroblast growth factor 23; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme.
Source: MSAC Executive meeting documents, December 2023.

The MSAC Executive reviewed the department's proposed descriptor and advised that the descriptor should be updated to align with the PBS listing for burosumab. The MBS item descriptor proposed by the MSAC Executive is presented in Table 3. Suggested additions (italics) and deletions (strikethrough) have been made by the assessment group.

[3] Trombetti A, Al-Daghri N, Brandi ML, Cannata-Andía JB, Cavalier E, Chandran M, Chaussain C, Cipullo L, Cooper C, Haffner D, Harvengt P, Harvey NC, Javaid MK, Jiwa F, Kanis JA, Laslop A, Laurent MR, Linglart A, Marques A, Mindler GT, Minisola S, Prieto Yerro MC, Rosa MM, Seefried L, Vlaskovska M, Belén Zanchetta M, Rizzoli R (2022) 'Interdisciplinary management of FGF23-related phosphate wasting syndromes: a consensus statement on the evaluation, diagnosis and care of patients with X-linked hypophosphataemia', Nat Rev Endocrinol, 18:366–384, doi:10.1038/s41574-022-00662-x.

Table 3 MBS item proposed by MSAC Executive for FGF-23 testing to determine eligibility for burosumab on the PBS

Category 6 – Pathology Services Group P2 – Chemical (to be confirmed)
Fibroblast growth factor 23, quantification in serum or plasma*, to confirm a diagnosis of X-linked hypophosphatemia,* if the service is requested by a specialist or consultant physician and the patient has: (i) current radiographic X-ray evidence of rickets or for those with growth plate fusion historical radiographic X-ray evidence of rickets~~ or current diagnosis of osteomalacia~~; and ~~(ii) a high pre-test probability of X-linked hypophosphatemia; and~~ ~~(iii)~~ *(ii)* a serum phosphate concentration below the age adjusted lower limit of normal; and ~~(iv)~~ *(iii)* 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.
Fee: $90 *Benefit: 75% = $67.50 85% = $76.50*

FGF-23 = fibroblast growth factor 23; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme.
Source: MSAC Executive meeting documents. Assessment group additions in italics and deletions in strikethrough.

The item descriptor proposed by the MSAC Executive restricted the service to use in patients who have met all other PBS clinical criteria required to access burosumab via a confirmed diagnosis of XLH (i.e. radiographic x-ray evidence of rickets, low serum phosphate, and renal phosphate wasting). However, the wording 'or current diagnosis of osteomalacia' is not present in the PBS restriction wording. According to correspondence provided by the department, this wording was added to the item descriptor to reflect that rickets is a sign of disease in children, and osteomalacia is the corollary adult diagnosis. The PBS listing appears to assume that for the adult population, historical radiographic x-ray evidence of rickets will be available. Whilst the additional wording in the proposed descriptor was intended to recognise osteomalacia diagnosis in adults, it does not align with the PBS listing and there is a risk that it will result in patients being tested for FGF-23 who are not eligible to receive burosumab on the PBS (if historical radiographic x-ray evidence of rickets is not available). As such, the assessment group suggested that 'or current diagnosis of osteomalacia' be deleted.

While the PBS restriction requires that the patient must be treated by a paediatric endocrinologist, paediatric nephrologist, endocrinologist, or nephrologist, the MBS item descriptor proposed by the MSAC Executive was consistent with the department's preference for the non-specific wording of 'specialist or consultant physician' rather than identifying each type of specialist.

The descriptor proposed by the MSAC Executive did not restrict use of the item to the diagnosis of XLH. To prevent the item being used for other purposes, such as monitoring FGF-23 levels, suggested italicised text ('to confirm the diagnosis of X-linked hypophosphatemia') has been added by the assessment group (Table 3). The assessment group also suggested the addition of wording such as that proposed by the department in Table 2, 'To determine eligibility for a treatment listed on the Pharmaceutical Benefits Schedule'.

The proposed descriptor places no limits on the frequency of FGF-23 testing. According to the Hypophosphatemic Working Party of the ANZBMS, FGF-23 testing would only be required once per lifetime to qualify for burosumab on the PBS. In some instances, however, a single repeat test may be required if the initial result is inconsistent with the clinical picture to exclude a laboratory mishap or analytical issue.

As patients may alternatively access burosumab on the PBS via a documented confirmation of PHEX pathogenic variant, the assessment group suggested that the item descriptor proposed by the MSAC Executive be amended to limit use to patients who do not have a documented confirmation of PHEX pathogenic variant. This would further restrict the population to those who require FGF-23 testing for access to burosumab on the PBS, in line with the original application.

Given that FGF-23 levels are influenced by phosphate and vitamin D therapy, the assessment group suggested that the item descriptor could include the requirement for patients to have ceased treatment for a specified timeframe prior to testing. Alternatively, an explanatory note about considerations for ceasing treatment prior to testing could be provided.

Removal of criterion (ii) from the descriptor proposed by the MSAC Executive is recommended by the Hypophosphatemic Working Party of the ANZBMS, given that patients who meet criteria (i), (iii) and (iv) inherently have a high pre-test probability of XLH. The PBS listing does not refer to patients with a high pre-test probability of XLH.

From a policy perspective, the detailed item descriptor proposed by the MSAC Executive increases the risk that patients may be billed privately for FGF-23 testing. If the pathology referral form does not contain sufficient information for the laboratory to confirm that all criteria in the MBS item descriptor have been met (e.g. x-ray evidence of rickets, low serum phosphate), the laboratory cannot bill the item to the MBS, and will instead bill the patient privately. In addition, the item may become unsuitable if there are changes to the PBS restrictions for burosumab.

If MSAC instead considers the simplified item descriptor proposed by the department (Table 2), the assessment group suggested that the descriptor should be amended to specify 'X-linked hypophosphatemia' rather than 'hypophosphatemia', in line with the population for burosumab. Alternatively, the department has suggested an even more simplified item descriptor of:

> 'Fibroblast growth factor 23, quantification in serum or plasma if the service is requested by a specialist or consultant physician to determine eligibility for a relevant treatment listed on the Pharmaceutical Benefits Schedule'.

Notably, this wording would not restrict use of the item to FGF-23 testing for access to burosumab but would provide flexibility around potential future changes to the PBS.

Proposed fee

The fee of $90 was tentatively proposed by the department based on the fee for FGF-23 testing at The Royal Children's Hospital Melbourne. This is based on the FGF-23 testing fee at Royal North Shore Hospital in Sydney (see Clinical Information PDF) – where the Royal Children's Hospital Melbourne samples are sent – and is consistent with the fee charged by Alfred Pathology.

Due to the small number of laboratories performing FGF-23 testing in Australia, the laboratory collecting the sample is often different to the laboratory performing the test. In this scenario the costs incurred by the laboratory collecting the sample are not included in the proposed item fee, as noted in consultation feedback from Australian Pathology that requested a higher fee, closer to $200 (see Summary of public consultation input).

There are a number of patient episode initiation (PEI) MBS items that may be applicable for the collecting laboratory to claim, as well as MBS items for management of bulk-billed services. MBS item 73940 relating to referral of a specimen may also be applicable to the laboratory receiving the specimen for testing.

A non-exhaustive search of existing MBS items for immunoassays for protein quantification found fees ranging from $14.55 (e.g. MBS item 71066) to $70.90 (e.g. MBS item 65150).

Shipping costs are not included in the MBS item fee and are not incorporated into the financial analysis. It is possible that these costs may be passed on to patients as an out-of-pocket expense.

7. Population

The proposed population is patients with a high pre-test probability of XLH, who meet all of the following criteria:

- current radiographic x-ray evidence of rickets, or for those with growth plate fusion, historical radiographic x-ray evidence of rickets
- a serum phosphate concentration below the age adjusted lower limit of normal
- 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.

FGF-23 testing is already available in Australia but is not publicly funded. It is proposed to be used in addition to existing tests to confirm diagnosis of XLH and eligibility for burosumab. Based on the MBS item descriptor proposed by the MSAC Executive (Table 3), FGF-23 testing would only be performed if a patient had met all other clinical criteria required to access burosumab on the PBS, therefore it is an additional test in the diagnostic pathway. Where FGF-23 testing demonstrates elevated (or inappropriately normal) serum or plasma FGF-23 levels of above the mean of the assay-specific reference range, the patient will have met all clinical criteria to access burosumab on the PBS.

According to the 2019 'Clinical practice recommendations for the diagnosis and management of XLH',[2] normal levels of FGF-23 should be interpreted as 'inappropriately normal' in patients who are hypophosphatemic, and in these patients, normal FGF-23 levels do not exclude a diagnosis of XLH. As all patients undergoing FGF-23 testing under the MBS item proposed by the MSAC Executive (Table 3) will have low phosphate levels as a pre-requisite, it is anticipated that only patients whose test results indicate low FGF-23 levels will not be eligible to receive burosumab on the PBS.

Existing MBS items appropriate to the prior tests undertaken to confirm a diagnosis of XLH are summarised in Table 4.

Table 4 Potential MBS items for confirming a diagnosis of XLH to access burosumab on the PBS

Criteria	Potential MBS items
Serum phosphate concentration, renal phosphate wasting	**66500** Quantitation in serum, plasma, urine or other body fluid (except amniotic fluid), by any method except reagent tablet or reagent strip (with or without reflectance meter) of: acid phosphatase, alanine aminotransferase, albumin, alkaline phosphatase, ammonia, amylase, aspartate aminotransferase, bicarbonate, bilirubin (total), bilirubin (any fractions), C-reactive protein, calcium (total or corrected for albumin), chloride, creatine kinase, creatinine, gamma glutamyl transferase, globulin, glucose, lactate dehydrogenase, lipase, magnesium, phosphate, potassium, sodium, total protein, total cholesterol, triglycerides, urate or urea - 1 test Fee: $9.70 Benefit: 75% = $7.30 85% = $8.25
	66503 2 tests described in item 66500 Fee: $11.65 Benefit: 75% = $8.75 85% = $9.95
	66506 3 tests described in item 66500 Fee: $13.65 Benefit: 75% = $10.25 85% = $11.65
X-ray evidence of rickets	**58306** Skeletal survey (R) Bulk bill incentive Fee: $96.85 Benefit: 75% = $72.65 85% = $82.35 (See para IN.0.19 of explanatory notes to this Category)[a]

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; R = services rendered at the request of another practitioner; XLH = X-linked hypophosphatemia.
a IN.0.19: Out-of-hospital services attract higher benefits when they are bulk billed by the provider. For all diagnostic imaging items (except those in Group 6 – Management of Bulk Billed Services and items 61369, 61466, 61485) benefits for bulk billed services are payable at 95% of the schedule fee for the item.
Source: MBS Online (accessed 23 May 2024).

Diagnosis of XLH can also be confirmed with genetic testing to identify a PHEX pathogenic variant, and this confirmation alone is sufficient to access burosumab on the PBS. This is considered an alternative diagnostic pathway, and where a pathogenic variant is identified, FGF-23 testing would not be required to access burosumab on the PBS. However, in patients who undergo PHEX testing and do not have a confirmed pathogenic variant (approximately 20% of XLH patients), FGF-23 testing may still be undertaken.

No downstream changes to the clinical pathway were anticipated if the proposed service is publicly funded. Based on public consultation feedback from the Clinical Practice and Therapeutics Committees of the ANZBMS, it is understood that patients who access burosumab on the PBS via a confirmed diagnosis of XLH with FGF-23 testing would still undergo PHEX testing for a more definitive diagnosis, although this would not be a requirement for PBS access.

Although FGF-23 testing enables access to burosumab on the PBS, lack of public funding was not anticipated to limit uptake given the relatively low cost of FGF-23 testing compared to the costs of accessing non-PBS burosumab.

Clinical guideline recommendations on FGF-23 testing for diagnosis of XLH

The recommendations provided in clinical guidelines and consensus statements regarding FGF-23 testing for XLH vary between guidelines, and do not always include FGF-23 testing as part of the essential testing for a diagnosis of XLH. Notably, these guidelines do not specifically relate to the diagnosis of XLH for the purpose of accessing treatment with burosumab.

The 2023 'Asia-Pacific consensus recommendations on X-linked hypophosphatemia'[1] propose that elevated or inappropriately normal FGF-23 may be used as an 'additional' criteria to support or further confirm the diagnosis of XLH in children (Statement 2B, GRADE: high quality) and adults (Statement 3B, GRADE: high quality), but do not include FGF-23 testing as an 'essential' criteria to confirm the diagnosis of XLH in children (Statement 2A, GRADE*:* high quality*)* or adults (Statement 3A, GRADE*:* high quality).

The 2019 'Clinical practice recommendations for the diagnosis and management of X- linked hypophosphataemia'[2] do not include FGF-23 testing in their recommendation regarding the initial diagnostic work-up for XLH. Confirming the clinical diagnosis of XLH by genetic analysis of the PHEX gene is recommended if feasible (grade B, moderate recommendation), and where genetic analysis is not available, elevated plasma levels of iFGF-23 and/or a positive family history for XLH support the diagnosis (grade C, moderate recommendation).

The 2022 'Interdisciplinary management of FGF23-related phosphate wasting syndromes: a consensus statement on the evaluation, diagnosis and care of patients with X-linked hypophosphataemia'[3] recommends that FGF-23 testing should be included in the evaluation of a patient with hypophosphatemia. Detecting inappropriately normal or elevated iFGF-23 levels using an intact FGF-23 assay is compatible with the diagnosis of FGF-23-mediated hypophosphatemia, of which XLH is one possible diagnosis.

8. Comparator

The alternative to FGF-23 testing is no testing and consequently no access to burosumab on the PBS.

Alternatively, genetic testing for a PHEX pathogenic variant to gain access to burosumab could be considered a comparator to FGF-23 testing. PHEX testing is funded on the MBS under several different items, for example item 73291 (see Table 5). The Hypophosphatemic Working Party of the ANZBMS have suggested that FGF-23 testing would be used preferentially to PHEX testing to gain access to burosumab on the PBS due to cost, accessibility and turnaround time. The Working Party advised that although PHEX testing is available in Australia, genetic counselling services and specialised testing laboratories have limited capacity, and accessing PHEX testing is particularly challenging for patients in rural and remote areas.

Table 5 MBS item relevant to PHEX testing

Category 6 – Pathology Services Group P7 – Genetics
73291 Analysis of one or more chromosome regions for specific constitutional genetic abnormalities of blood or fresh tissue in a) diagnostic studies of a person with developmental delay, intellectual disability, autism, or at least two congenital abnormalities, in whom cytogenetic studies (item 73287 or 73289) are either normal or have not been performed; or b) studies of a relative for an abnormality previously identified in such an affected person. - 1 or more tests.
Fee: $230.95 **Benefit**: 75% = $173.25 85% = $196.35

PHEX = phosphate-regulating endopeptidase homolog X-linked.
Source: MBS Online (Accessed 30 May 2024).

Comparative safety and effectiveness were not in scope for the assessment of this application.

9. Summary of public consultation input

Consultation input was received from three (3) professional organisations:

- Public Pathology Australia (PPA) - targeted
- Australian Pathology (AP)
- Australia and NZ Bone and Mineral Society (ANZBMS)

Benefits

- Significant improvements in quality of life (stiffness, muscle and bone pain and physical function) with burosumab, which is now available on the PBS for the treatment of XLH.
- Equity of access, for patients in lower socio-economic groups who would greatly benefit from treatment with burosumab.
- The test would rapidly rule out patients with non-FGF-23 causes of kidney phosphate wasting who would otherwise require more expensive diagnostic services such as gallium-Dotatate PET imaging.
- Enable testing of family members of patients with confirmed XLH who also demonstrate a reduced phosphate leading to a more accurate recognition of this disorder.

No disadvantages were identified by the organisations that provided consultation input.

Comments

The input received provided feedback on the process and estimated cost of the testing.

Australian Pathology commented that there is very limited demand for this specific test which is typically only performed by a small number of reference laboratories who do not run collection centres. Public Pathology Australia specified that some laboratories may run the test on the Diasorin Liaison immunoassay platform, and that particular platforms should not be named in the MBS item descriptors.

Public Pathology Australia supported the proposed test fee of $90.00, as it is in line with member costs and noted it may be performed in a specialised setting which typically is more expensive. The Clinical Practice and Therapeutics Committees of the ANZBMS were similarly supportive of the proposed fee, noting that it was consistent with the cost recovery required at the current sample volume for FGF-23 testing. Australian Pathology advised that a more suitable fee for the

whole process of testing (collecting, freezing, and transporting the sample to the reference laboratory performing the test) should be nearer to $200. Australian Pathology also reported that a fee of $111.10 was charged by Royal North Shore Hospital to perform the test (higher than the $90 listed on the NSW Health Pathology website).

10. Characteristics of the evidence base

A systematic evaluation of the evidence base for FGF-23 testing was not in scope for the assessment of this application.

11. Comparative safety

An evaluation of the comparative safety of FGF-23 testing was not in scope for the assessment of this application. Adverse events are expected to be the same as those associated with a standard blood test.

12. Comparative effectiveness

A full evaluation of the comparative clinical effectiveness of FGF-23 testing was not in scope for the assessment of this application. A brief summary of relevant clinical evidence has been presented.

Key evidence informing clinical guidelines

The key evidence referenced in clinical guidelines was reviewed, and information relevant to the current application has been summarised below.

A retrospective review reported the clinical and molecular features of 153 Chinese patients with XLH who were identified with PHEX gene mutations from 2008 to 2019[4]. Sixty-two patients had serum iFGF-23 values determined, with 96.8% (30/31) of paediatric patients and 74.2% (23/31) of adult patients recording a high level (>42.2 pg/mL). The proportion of paediatric patients with high levels of circulating iFGF-23 was higher than that of adult patients (P = 0.026). Low serum iFGF-23 (<16.1 pg/mL) was recorded in one adult patient (3.2%) and no paediatric patients. The median (range) for serum iFGF-23 in all 62 patients was 91.88 pg/mL (14.39 to 730.70 pg/mL). It is unclear whether the patients were on treatment at the time of iFGF-23 testing.

A similar retrospective review reported 261 patients with clinical features of XLH and known or novel mutations in the PHEX gene, followed at Peking Union Medical College Hospital from 2005 to 2017[5]. Serum samples collected at the patient's initial visit were available for iFGF-23 analysis for 233 patients. A two-site ELISA kit (KAINOS Laboratories, Inc., Tokyo, Japan) was used for iFGF-23 analysis. Serum iFGF-23 levels were high in 91.9% of patients (upper limit of reference range 42.2 pg/mL). It is unclear how many patients had an iFGF-23 level in the normal and low range.

[4] Lin X, Li S, Zhang Z, Yue H (2021) 'Clinical and genetic characteristics of 153 Chinese patients with X-linked hypophosphatemia', Frontiers in Cell and Developmental Biology, 9:617738, doi:10.3389/fcell.2021.617738.

[5] Zhang C, Zhao Z, Sun Y, Xu L, JiaJue R, Cui L, Pang Q, Jiang Y, Li M, Wang O, He X, He S, Nie M, Xing X, Meng X, Zhou X, Yan L, Kaplan JM, Insogna KL, Xia W (2019) 'Clinical and genetic analysis in a large Chinese cohort of patients with X-linked hypophosphatemia', Bone, 121:212-220, doi:10.1016/j.bone.2019.01.021.

Other studies reviewed included only small numbers of patients with XLH (≤8) or were designed to examine the clinical utility of a specific FGF-23 assay.

Clinical evidence considered by the PBAC for burosumab

The key clinical studies of burosumab considered by the PBAC were one randomised trial in the paediatric population (NCT02915705) and one randomised trial in the adult population (NCT02526160). Additional studies were included as supportive evidence.

Eligibility criteria relating to PHEX mutation status and FGF-23 levels from the published evidence included in the PBAC application are summarised in Table 6 for the paediatric population and Table 7 for the adult population.

The inclusion criteria for the key paediatric RCT required patients to have a confirmed PHEX mutation or variant of unknown significance in the patient or a family member with appropriate X-linked dominant inheritance, but did not require FGF-23 testing. Only one of the two supportive published studies allowed serum iFGF-23 testing as an alternative to PHEX testing for eligibility.

In the key adult RCT, the inclusion criteria required the patient to have a documented PHEX mutation in either the patient or in a directly related family member with appropriate X-linked inheritance, or a serum iFGF-23 level > 30 pg/mL by the Kainos assay. The three published supportive studies all allowed serum iFGF-23 testing for eligibility.

Notably, all studies that included FGF-23 testing in the eligibility criteria used serum samples and measured iFGF-23.

Table 6 PHEX and FGF-23 eligibility criteria and status for published paediatric studies in May 2022 PBAC submission

Trial Study design Number of participants	PHEX and/or FGF-23 eligibility criteria	PHEX mutation positive – number (%)	Elevated FGF-23 – number (%)
Imel (2019) NCT02915705 RCT (burosumab vs. conventional therapy) N=61	Confirmed PHEX mutation or variant of unknown significance in the patient or a family member with appropriate X-linked dominant inheritance	61 (100%) *Of the excluded patients (n = 61), < 3 were excluded due to failure to meet the PHEX criteria*	N/A
Carpenter (2018) Dose finding RCT (2 vs 4 weeks burosumab) N=52	Presence of the PHEX mutation in the patient or a directly related family member, or a serum iFGF-23 level of > 30 pg/mL	45 (87%) - pathogenic PHEX mutations	7 patients not positive for pathogenic PHEX mutations (1 probably pathogenic, 4 of unknown significance, 2 no mutation); all had baseline serum iFGF-23 > 30 pg/mL
Whyte (2019) Single-arm study N=13	Confirmed PHEX mutation or a variant of unknown significance in the patient or direct relative also affected with XLH	13 (100%)	N/A

FGF-23 = fibroblast growth factor 23; iFGF-23 = intact FGF-23; N/A = not applicable; PBAC = Pharmaceutical Benefits Advisory Committee; PHEX = phosphate-regulating endopeptidase homolog X-linked; RCT = randomised controlled trial; XLH = X-linked hypophosphatemia.

Table 7 PHEX and FGF-23 eligibility criteria and status for published adult studies in May 2022 PBAC submission

Trial Study design Number of participants	PHEX and/or FGF-23 eligibility criteria	PHEX mutation positive – number (%)	Elevated FGF-23 – number (%)
Insogna (2018) NCT02526160 Placebo-controlled RCT N=134	Documented PHEX mutation in either the patient or in a directly related family member with appropriate X-linked inheritance and/or serum iFGF-23 level > 30 pg/mL by the Kainos assay	Pathogenic: 95 (71%) Likely pathogenic: 15 (11%) Variant of uncertain significance: 17 (13%)	In the 7 patients with no PHEX mutation, it is assumed that serum iFGF-23 was > 30 pg/mL to meet the inclusion criteria
Insogna (2019) Single-arm study N=14	Documentation of a PHEX mutation or a serum iFGF-23 level > 30 pg/mL	NR *Of the 11 excluded patients, none were excluded on the basis of PHEX/iFGF-23 status*	NR
Carpenter (2014) Placebo-controlled single dose RCT N=38	Serum iFGF-23 ≥ 30 pg/mL	N/A	38 (100%)
Imel (2015)# Single-arm study N=30	Serum iFGF-23 > 30 pg/mL	N/A	30 (100%)

FGF-23 = fibroblast growth factor 23; iFGF-23 = intact FGF-23; N/A = not applicable; NR = not reported; PBAC = Pharmaceutical Benefits Advisory Committee; PHEX = phosphate-regulating endopeptidase homolog X-linked; RCT = randomised controlled trial.
A subgroup of this study cohort was included in an extension study included in the May 2022 PBAC submission.
Source: original publications (see DCAR References).

13. Economic evaluation

An economic evaluation was not in scope for the assessment of this application.

14. Financial/budgetary impacts

An epidemiological approach was taken to estimate the financial implications to the MBS of the proposed service, FGF-23 testing for paediatric and adult patients with a high pre-test probability of XLH.

Paediatric population

The prevalent paediatric XLH population was estimated at 110 patients in 2023, calculated using a prevalence of 1.91 per 100,000 children[6]. FGF-23 testing is for access to burosumab; therefore, the eligible population for the test is the burosumab treatment naïve population. This

[6] Sandy JL, Nunez C, Wheeler BJ, Jefferies C, Morris A, Siafarikas A, Rodda CP, Simm P, Biggin A, Aum S,Elliot EJ, Munns CF (2023) 'Prevalence and characteristics of paediatric X-linked hypophosphataemia in Australia and New Zealand: results from the Australian and the New Zealand Paediatric Surveillance Units survey', Bone, 173:116791, doi:10.1016/j.bone.2023.116791.

was estimated by removing 61 patients who accessed burosumab under the early access program, leaving 49 eligible patients. Applying a burosumab uptake rate of 80% to the eligible population, it was estimated that there would be 39 patients accessing testing for burosumab eligibility in 2023–24 (following PBS listing of burosumab and in the absence of MBS funding for FGF-23 testing). The 10 patients not accessing testing for burosumab eligibility in that year were considered eligible for FGF-23 testing in the subsequent year, along with an incident population of 12 patients per year. The analysis also assumed that a proportion of paediatric XLH patients would access burosumab through identification of a PHEX pathogenic variant, with the proportion of patients accessing burosumab through PHEX testing declining over time. Therefore, the eligible population was estimated to be very small, approximately 12 paediatric patients per year.

The financial implications to the MBS resulting from the proposed listing of FGF-23 testing for access to burosumab in the paediatric population are summarised in Table 8.

Table 8 Financial implications to the MBS of FGF-23 testing for access to burosumab (paediatric)

Parameter	FY 2024-25	FY 2025-26	FY 2026-27	FY 2027-28	FY 2028-29	FY 2029-30
Number of new patients with XLH (i.e. babies born)[a]	12	12	12	12	12	12
Additional eligible patients from previous year[b]	10	2	1	1	0	0
Number of burosumab naïve patients[c]	22	14	13	13	13	12
Burosumab uptake rate	90%	95%	96%	97%	98%	98%
Number of patients seeking access to burosumab[d]	20	14	12	12	12	12
Proportion of patients accessing burosumab through PHEX testing	32%	16%	8%	4%	2%	1%
Number of patients accessing burosumab through PHEX testing[e]	6	2	1	0	0	0
Total number of patients having FGF-23 testing[f]	13	12	11	12	12	12
Change in cost to the MBS						
Cost to the MBS (85% benefit)[g] of proposed item for FGF-23 testing	$995	$918	$842	$918	$918	$918

FGF-23 = fibroblast growth factor 23; FY = financial year; MBS = Medicare Benefits Schedule; PHEX = phosphate-regulating endopeptidase homolog X-linked; XLH = X-linked hypophosphatemia.
a Calculated by multiplying the incidence of XLH (0.0039%) by the number of live births in Australia in 2021 (313,407).
b Difference between number of patients eligible for FGF-23 testing and number of patients accessing burosumab through FGF-23 testing in the previous year.
c Calculated by adding number of new patients with XLH with number of additional eligible patients from the previous year.
d Calculated by multiplying number of burosumab naïve patients by burosumab uptake rate.
e Calculated by multiplying number of patients seeking access to burosumab with proportion of patients accessing burosumab through PHEX testing.
f Difference between number of patients seeking access to burosumab and number of patients accessing burosumab through PHEX testing.
g Calculated using 85% benefit ($76.50) for proposed MBS item.
Note: Apparent discrepancies may be due to rounding with small patient numbers.
Source: DCAR Table 13.

Adult population

The prevalent adult population was estimated at 277 patients in the 2023–24 financial year, calculated using a prevalence rate of 13.3 per million adults[7]. The burosumab uptake rate in adults following PBS listing of burosumab was estimated to be 25%, leaving a burosumab treatment naïve population of 208 patients at the start of the 2023–24 financial year. Applying a burosumab uptake rate of 30% to the eligible population, it was estimated there would be 62 patients accessing testing for burosumab eligibility in 2023–24 (in the absence of MBS funding for FGF-23 testing). The patients not accessing testing for burosumab eligibility that year were considered eligible for FGF-23 testing in the subsequent year, along with the additional patients with XLH due to population growth (1.8%).

The uptake of the proposed service declines as the XLH prevalent population is more likely to have already accessed burosumab. The financial implications to the MBS resulting from the proposed listing of FGF-23 testing for access to burosumab in the adult population are presented in Table 9.

Table 9 Financial implications to the MBS of FGF-23 testing for access to burosumab (adult)

Parameter	FY 2024-25	FY 2025-26	FY 2026-27	FY 2027-28	FY 2028-29	FY 2029-30
Number of adult patients with XLH[a]	282	287	292	298	303	309
Number of burosumab naïve patients[b]	150	103	67	42	26	17
Burosumab uptake rate	35%	40%	45%	50%	55%	60%
Number of patients seeking access to burosumab[c]	53	41	30	21	15	10
Proportion of patients accessing burosumab through PHEX testing	16%	8%	4%	2%	1%	0%
Number of patients accessing burosumab through PHEX testing[d]	8	3	1	0	0	0
Total number of patients having FGF-23 testing[e]	44	38	29	21	14	10
Change in cost to the MBS						
Cost to the MBS (85% benefit)[f] of proposed item for FGF-23 testing	$3,366	$2,907	$2,219	$1,607	$1,071	$765

FGF-23 = fibroblast growth factor 23; FY = financial year; MBS = Medicare Benefits Schedule; PHEX = phosphate-regulating endopeptidase homolog X-linked; XLH = X-linked hypophosphatemia.
a Calculated using annual population growth of 1.8%.
b Calculated using the growth in number of adult patients with XLH and the number of burosumab naïve patients remaining from the previous year (e.g. [282-277]+[208-62]).
c Calculated by multiplying the number of burosumab naïve patients with the burosumab uptake rate.
d Calculated by multiplying the number of patients seeking access to burosumab by the proportion of patients accessing burosumab through PHEX testing.
e Difference between the number of patients seeking access to burosumab and the number of patients accessing burosumab through PHEX testing.
f Calculated using 85% benefit ($76.50) for proposed MBS item
Source: DCAR Table 14.

[7] Hawley S, Shaw NJ, Delmestri A, Prieto-Alhambra D, Cooper C, Pinedo-Villanueva R, Javaid MK (2020) 'Prevalence and mortality of individuals with X-linked hypophosphatemia: a United Kingdom real-world data analysis', J Clin Endocrinol Metab, 105(3):e871–8. doi:10.1210/clinem/dgz203.

Reduction of uncertainty

A range of analyses were undertaken to explore the uncertainty associated with the item fee, prevalence of XLH, the uptake rate of burosumab, and the proportion of patients accessing burosumab via PHEX testing compared to FGF-23 testing. Although these generally increased the impact to the MBS, the pattern of declining or stable impact remained; in none of the analyses undertaken did the cost to the MBS exceed $9,000 in a single year for the adult population.

Although MBS funding for FGF-23 testing could result in reduced PHEX testing for access to burosumab (due to substitution by FGF-23) and a consequent reduction in overall costs to the MBS, the likelihood of this scenario is uncertain. Consultation feedback from the Clinical Practice and Therapeutics Committees of the ANZBMS suggested that patients who accessed burosumab on the PBS via a confirmed diagnosis of XLH (including high or inappropriately normal FGF-23) would still undergo PHEX testing as part of the diagnostic process.

15. Other relevant information

Nil

16. Applicant comments on MSAC's Public Summary Document

The Hypophosphatemic Working Party of the Australian and New Zealand Bone and Mineral Society strongly supports the outcome of making FGF-23 testing available for the diagnosis of XLH.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website