**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Health Technology Appraisal**

# Burosumab for treating FGF23-related hypophosphataemia in tumour-induced osteomalacia

**Draft scope**

## Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of burosumab within its marketing authorisation for treating FGF23-related hypophosphataemia in tumour-induced osteomalacia.

## Background

Tumour-induced osteomalacia is a rare disease which is characterised by bone pain, fractures and muscle weakness. It is caused by excessive production of fibroblast growth factor 23 (FGF23) by tumour cells, which causes abnormal processing of phosphate in the kidneys and consequently, loss of phosphate in the urine. This results in low levels of phosphate in the blood (hypophosphataemia) which can lead to soft, weak bones (osteomalacia). As a result of excess FGF23, people frequently develop secondary hyperparathyroidism[1]. Many people also develop sarcopenia or severe sarcopenia[2].

Tumour-induced osteomalacia typically occurs in adults and is equally common in males and females[1]. The average age of diagnosis is 40 to 45 years old, but tumour-induced osteomalacia has also been reported in children[1]. The non-specific symptoms of fatigue, muscle weakness, bone pain and multiple fractures can lead to a delay in diagnosis[4]. Children can present with bone pain, skeletal deformities, and growth retardation[1]. The time between symptom onset and diagnosis ranges from 2.5 to 28 years[1]. People with tumour-induced osteomalacia can experience moderate pain which negatively impacts walking, general activities, work, and mood[2].

There is a lack of data on prevalence and incidence of tumour-induced osteomalacia. In England (2020-2021), there were 5 episodes where people received consultant care and 1 hospital admission with a primary diagnosis of other adult osteomalacia[4].

The only treatment that targets the underlying cause of FGF23-related hypophosphataemia in tumour-induced osteomalacia is complete surgical removal of the tumour[1]. This is not always possible because tumours are typically very small in size, so locating them is difficult. Some tumours are in locations that mean that surgery is not possible. Image-guided ablation with radiofrequency or cryoablation provides an alternative treatment but long-term outcomes are unknown[1]. There is no consensus on the management of unresectable FGF23-related hypophosphataemia in tumour-induced osteomalacia however options include phosphate supplementation, vitamin D analogues such as alfacalcidol or calcitriol, or supportive care[1]. Conventional therapy is taken 4-6 times a day which interferes with usual activities including work and can disturb sleep. Treatment continues for as long as the tumour is not identified or resected[5]. Management of unresectable FGF23-related hypophosphataemia in tumour-induced osteomalacia differs across treatment centres, for example phosphate is not always offered to adults without fractures because of the risks of treatment-related complications such as hyperparathyroidism.

However, most people with unresectable FGF23-related hypophosphataemia in tumour-induced osteomalacia receive treatment. Corrective surgery of skeletal deformities and joint replacements may be required.

## The technology

Burosumab (Crysvita, Kyowa Kirin) is an anti-FGF23 human monoclonal antibody which improves phosphate homeostasis by targeting excess FGF23. Burosumab binds to FGF23 rendering it inactive, and thereby restores renal tubular reabsorption of phosphate and increases the production of 1,25-dihydroxyvitamin D which enhances intestinal absorption of calcium and phosphate. Burosumab is administered by subcutaneous injection.

Burosumab does not currently have a marketing authorisation in the UK for treating FGF23-related hypophosphataemia in tumour-induced osteomalacia. It has been studied in adults with FGF23-related hypophosphataemia in tumour-induced osteomalacia in clinical trials that have a single arm (no comparator).

Burosumab has a marketing authorisation in the UK for the treatment of X-linked hypophosphataemia in children (ages 1-17) and in adults.

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| **Intervention(s)** | Burosumab |
| **Population(s)** | Adults with FGF23-related hypophosphataemia in tumour-induced osteomalacia who have tumours that cannot be surgically removed. |
| **Comparators** | Established clinical management without burosumab (including vitamin D analogues and phosphate supplementation) |
| **Outcomes** | The outcome measures to be considered include:<br>• fractures<br>• pain (including bone pain, joint pain and joint stiffness)<br>• motor skills<br>• tooth loss and pain<br>• neurological complications (including problems with hearing and balance, and spinal cord compression)<br>• renal function<br>• parathyroid hormone levels<br>• alkaline phosphatase levels<br>• mortality<br>• adverse effects of treatment<br>• health-related quality of life (for patients and carers). |

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| **Economic analysis** | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.<br><br>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.<br><br>Costs will be considered from an NHS and Personal Social Services perspective. |
| **Other considerations** | Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. |
| **Related NICE recommendations and NICE Pathways** | Related Technology Appraisals:<br><br>Burosumab for treating X-linked hypophosphataemia in children and young people (2018) NICE highly specialised technology guidance 8.<br><br>In development:<br><br>Burosumab for treating X-linked hypophosphataemia in adults. NICE technology appraisal guidance. Publication date to be confirmed.<br><br>Related Guidelines:<br><br>None<br><br>Guidelines in development<br><br>None<br><br>Related Interventional Procedures:<br><br>None<br><br>Related Public Health Guidance/Guidelines:<br><br>None<br><br>Related Quality Standards:<br><br>None<br><br>Related NICE Pathways:<br><br>None |

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| **Related National Policy** | The NHS Long Term Plan, 2019. NHS Long Term Plan<br>NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019)<br>Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 2,4,5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017<br>https://www.england.nhs.uk/wp-content/uploads/2017/10/prescribed-specialised-services-manual.pdf |

**Questions for consultation**

What is the population size of adults and children with FGF23-related hypophosphataemia in tumour-induced osteomalacia who have tumours that cannot be located or surgically removed?

Are people with FGF23-related hypophosphataemia in tumour-induced osteomalacia, who have tumours that cannot be located, clinically distinct from people with other forms of acquired FGF23 excess?

Do all tumours cause tumour-induced osteomalacia or just specific types? If multiple tumours can be causal, is it possible to diagnose the specific type of tumour causing the tumour-induced osteomalacia?

Which treatments are considered to be established clinical practice in the NHS for FGF23-related hypophosphataemia in tumour-induced osteomalacia who have tumours that cannot be located or surgically removed?

Have all relevant comparators for burosumab been included in the scope?
If applicable, 'How should best supportive care be defined?'

Are the outcomes listed appropriate?

Are there any subgroups of people in whom burosumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which burosumab will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider burosumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of burosumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

**References**


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2. Jerkovich, F., Nuñez, S., Mocarbel, Y., Pignatta, A., Elías, N., Cassinelli, H., Díaz, A.G, Vigovich, C., Balonga, M.C., Cohen, A.C., Mumbach, G., Gonzalez, S., Zanchetta, J.R., Zanchetta, M.B. 2021. Burden of disease in patients with tumor-induced osteomalacia. *American Society for Bone and Mineral Research.* E10436. DOI:10.1002/jbm4.10436.
3. Feng, J., Jiang, Y., Wang, O., Li, M., Xing, X., Huo, L., Li, F., Yu, W., Zhong, D-R., Jin, J., Liu, Y., Qi, F., Lv, W., Zhou, L., Meng, X-W., Xia, W-B. 2017. The diagnostic dilemma of tumor induced osteomalacia: a retrospective analysis of 144 cases*. Endocrine Journal*. 28: 675-683. DOI:10.1507/endocrj.EJ16-0587.
4. NHS Digital. *Hospital Admitted Patient Care Activity, 2020-2021.* 2021. Available from: Hospital Admitted Patient Care Activity 2020-21 - NHS Digital. [Accessed 03 February 2022].
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