Technology Guidance

Burosumab

for treating X-linked hypophosphataemia

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

- ✓ Burosumab 10 mg/mL, 20 mg/mL and 30 mg/mL solution for injection for treating X-linked hypophosphataemia (XLH) in adults and children 1 year of age and older, in line with the following criteria:
  - Patient must have a documented confirmation of PHEX pathogenic variant; or
  - Patient must have a confirmed diagnosis of XLH demonstrated by the presence of all of the following:
    - a serum phosphate concentration below the age adjusted lower limit of normal;
    - current or historical (for those with growth plate fusion) radiographic X-ray evidence of rickets;
    - 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
  - Patient must be treated by, or in consultation with, a specialist physician experienced in the diagnosis and management of XLH.

Funding status

Burosumab 10 mg/mL, 20 mg/mL and 30 mg/mL solution for injection are recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indication from 1 August 2024.

Published: 4 Jun 2024

Factors considered to inform the recommendations for funding

Technology evaluation

1.1. At the March 2024 meeting, the MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of burosumab for treating X-linked hypophosphataemia (XLH) in children and adults. The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical experts from public healthcare institutions. Published clinical and economic evidence for burosumab was considered in line with its registered indication.

1.2. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost-effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.3. Additional factors, including social and value judgments, may also inform the Committee's funding considerations.

Clinical need

2.1. XLH is a genetic disease that causes abnormal bone mineralisation, leading to rickets, osteomalacia, stunted growth, fractures, and skeletal deformities such as bowed legs. Patients with this condition have impaired mobility and may require surgery to correct bone deformities. XLH is caused by mutations in the PHEX gene, leading to excess levels of fibroblast growth factor 23 (FGF23), a hormone that regulates phosphate. This results in low serum levels of phosphate and active vitamin D, both of which are essential for normal bone formation.

2.2. In Singapore, there are at least 20 patients who have been diagnosed with XLH. Currently, patients may receive conventional therapy which comprises supplements of oral phosphate and active vitamin D. However, these may not be sufficient for correcting the biochemistry of XLH or for managing its symptoms. Long-term use of conventional therapy has also been associated with adverse effects such as nephrocalcinosis and hyperparathyroidism.

2.3. The Committee acknowledged that conventional therapy for XLH was suboptimal and there was a high clinical need for effective treatments. They noted that burosumab is the only HSA-approved therapy that targets the underlying pathophysiology of XLH by binding and inhibiting excess FGF23. Hence, burosumab may be considered for funding to improve treatment affordability and ensure appropriate patient care.

Clinical effectiveness and safety

3.1. The Committee reviewed the clinical evidence from two phase III randomised controlled trials involving burosumab for the treatment of XLH in children (CL301) and adult (CL303) populations.

3.2. In the CL301 trial, 61 children were randomly assigned to receive burosumab or conventional therapy for 64 weeks. Results showed that burosumab was more effective than conventional therapy in normalising phosphate homeostasis, improving healing of rickets, and improving growth and mobility in children.

3.3. In the CL303 trial, 134 adults were randomised to receive burosumab or placebo for 24 weeks. Results showed that burosumab provided a sustained increase in serum phosphate levels compared with placebo. Burosumab was also associated with improved fracture healing, increased biomarkers of bone formation and resorption, and reduced stiffness. After 24 weeks, all patients received burosumab in an open-label treatment continuation period. At week 48, results showed that burosumab led to a sustained correction of serum phosphate levels and continued healing of fractures.

3.4. The Committee agreed that burosumab provided meaningful clinical benefits and had an acceptable safety profile in children and adults with XLH. Based on available clinical data, burosumab was not associated with adverse effects of nephrocalcinosis and hyperparathyroidism, in contrast to conventional therapy.

Cost effectiveness

4.1. The Committee reviewed the economic evaluations from overseas HTA agencies, which reported high incremental cost-effectiveness ratios (ICERs) when burosumab was compared with conventional therapy in patients with XLH. However, the ICERs were noted to be uncertain due to various factors such as limited data on the long-term efficacy of burosumab and uncertainties in the model structure. Therefore, the agencies required price reductions and risk-sharing arrangements to address the uncertainty in the evidence and improve the cost effectiveness of burosumab.

4.2. When compared with prices in overseas reference jurisdictions, the Committee considered burosumab likely to represent an acceptable use of healthcare resources for treating XLH in the local setting. The Committee also acknowledged that the company's pricing proposal was adequate to manage the uncertainty of the overall budget impact.

Estimated annual technology cost

5.1. The Committee noted that the annual cost impact to the public healthcare system was estimated to be between SG$1 million and SG$3 million in the first year, and between SG$3 million and SG$5 million in the fifth year of listing burosumab on the MOH List of Subsidised Drugs for treating XLH.

Recommendations

6.1. Based on available evidence, the Committee recommended burosumab 10 mg/mL, 20 mg/mL and 30 mg/mL solution for injection be listed on the Medication Assistance Fund (MAF) for treating XLH in adults and children 1 year of age and older. This decision was based on the high clinical need and acceptable clinical effectiveness of burosumab, and given that the treatment is considered to be an acceptable use of healthcare resources in Singapore.