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# Denosumab

*for the prevention of skeletal-related events in adults with bone metastases from solid tumours*

Technology Guidance from the MOH Drug Advisory Committee

## Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has not recommended denosumab to be listed on the Medication Assistance Fund (MAF) for the prevention of skeletal-related events in adults with bone metastases from solid tumours as it does not reflect a cost-effective use of healthcare resources at the price proposed by the manufacturer.

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## Factors considered to inform the recommendations for subsidy

### Technology evaluation

- 1.1 The MOH Drug Advisory Committee (“the Committee”) considered the evidence presented for the technology evaluation of denosumab for prevention of skeletal-related events (SREs) in adults with bone metastases from solid tumours. The Agency for Care Effectiveness conducted the evaluation in consultation with clinical experts from the public healthcare institutions. Published clinical and economic evidence for denosumab was considered in line with the registered indication, and for patient subgroups who have an unmet need (that is, patients who are unable to receive bisphosphonates).
- 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
  - 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 subsidy considerations.

### Clinical need

- 2.1 Denosumab is considered by local clinicians as a second-line treatment option for patients with bone metastases from solid tumours, after the use of bisphosphonates. For patients in whom bisphosphonates are contraindicated, including patients with renal impairment, denosumab may be considered in clinical practice as a possible first-line therapeutic option. The number of patients likely to require treatment for bone metastases in Singapore each year across all types of solid tumours is small.

## Clinical effectiveness and safety

- 3.1 The Committee agreed that zoledronic acid and pamidronate, which are both listed on MAF, were the appropriate comparators for denosumab for the prevention of SREs in adults with bone metastases from solid tumours.
- 3.2 The Committee noted that the pivotal trials showed that:
  - Denosumab was superior to zoledronic acid in delaying time to first on-study SRE and reducing the risk of developing multiple SREs in patients with breast cancer or castrate-resistant prostate cancer.
  - Denosumab was also shown to be non-inferior to zoledronic acid in patients with other solid tumours or multiple myeloma.
- 3.3 However, as the primary outcome of SREs measured in the trials was a composite endpoint, the Committee was mindful that the individual components of this endpoint may not all be clinically meaningful, therefore results should be interpreted with caution.
- 3.4 The Committee noted that in Singapore denosumab is typically used when bisphosphonates have failed or are contraindicated (e.g. creatinine clearance less than 30 ml/min). However, evidence to support the use of denosumab in this setting is also limited.
- 3.5 The Committee also acknowledged that the rates of severe adverse events were similar between zoledronic acid and denosumab.

## Cost effectiveness

- 4.1 The Committee considered the cost-effectiveness of denosumab from published studies and noted that there were no local economic evaluations available. It acknowledged that economic evidence from the UK showed that the cost effectiveness of denosumab varied widely when compared with branded zoledronic acid depending on the particular patient groups that treatment was targeted to, and many incremental cost-effectiveness ratios (ICERs) were above the range which would normally be considered an acceptable use of healthcare resources. It further noted that based on these evaluations, NICE (UK) had only recommended the use of denosumab in patients with bone metastases from solid tumours other than prostate cancer, following a confidential price discount being agreed by the manufacturer.

- 4.2 The Committee concluded that at the price proposed by the manufacturer, denosumab was unlikely to be cost effective in Singapore, even if its use was restricted to patients who are unable to receive bisphosphonates, as generic zoledronic acid is now available, leading to a large price difference between the agents. Even at the discounted price proposed by the manufacturer, the cost of denosumab was more than five times higher than zoledronic acid.

## Estimated annual technology cost

- 5.1 The Committee estimated that around 150 people with bone metastases in Singapore would benefit from Government assistance for denosumab. The annual cost impact was estimated to be less than \$1 million in the first year of listing on the MAF.
- 5.2 The Committee was mindful that although current usage of denosumab is relatively low, subsidy will increase its use and in turn could have a considerable impact on the healthcare budget.

## Recommendation

- 6.1 On the basis of the evidence available, the Committee did not recommend denosumab 120 mg vial for listing on the MAF for the prevention of SREs in adults with bone metastases from solid tumours, due to unacceptable cost-effectiveness given its high cost compared with generic alternative treatment options.

### About the Agency

The Agency for Care Effectiveness (ACE) is the national health technology assessment agency in Singapore residing within the Ministry of Health. It conducts evaluations to inform the subsidy of treatments, and produces guidance on the appropriate use of treatments for public hospitals and institutions in Singapore. When using the guidance, the responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

Find out more about ACE at [www.ace-hta.gov.sg/about](http://www.ace-hta.gov.sg/about)

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