Denosumab

for the treatment of postmenopausal women with osteoporosis at high risk of fracture

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

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

✓ Denosumab 60 mg pre-filled syringe for the treatment of osteoporosis (T-score ≤ -2.5) in post-menopausal women at high risk of fracture, who:
  ▪ have a renal function eGFR > 30 ml/min, and
  ▪ are unable to tolerate or follow the administration instructions for oral bisphosphonates.

Patients must also receive adequate calcium and vitamin D supplementation whilst undergoing treatment.

Subsidy status

Denosumab 60 mg pre-filled syringe is recommended for inclusion on the Medication Assistance Fund (MAF) in line with the abovementioned criteria.

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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 the treatment of men and postmenopausal women with osteoporosis at high risk of fracture. The Agency for Care Effectiveness conducted the evaluation, in consultation with clinical experts from the public healthcare institutions. The evaluation considered the use of denosumab as a first-line treatment for osteoporosis, with particular focus on patient subgroups who have an unmet clinical need and in whom denosumab offers an effective treatment option in clinical practice (that is, patients who are unable to receive oral 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 the preferred second-line therapeutic option for the treatment of osteoporosis in both men and postmenopausal women, after oral bisphosphonates.

2.2 In local clinical practice, only patients who have renal impairment, expected gastrointestinal intolerance to bisphosphonates or contraindication to bisphosphonates receive denosumab as first-line therapy due to its high cost compared with generic oral bisphosphonates.

2.3 There are approximately 2000 patients treated with denosumab for osteoporosis in Singapore every year. The majority of denosumab use is for the treatment of postmenopausal women, and only 10-15% of utilisation is in men.
Clinical effectiveness and safety

3.1 The Committee agreed that intravenous zoledronic acid, which is listed on the MAF was the appropriate comparator for denosumab for the treatment of osteoporosis.

3.2 The Committee noted that there were no head-to-head trials comparing denosumab with zoledronic acid as first-line therapy. Thus, results from the FREEDOM placebo-controlled trial conducted in postmenopausal women were accepted to inform the use of denosumab for osteoporosis. The FREEDOM trial showed that denosumab was effective in reducing the risk of new vertebral fractures (NNT=21), and delaying time to first non-vertebral fracture (NNT=67) and hip fracture (NNT=334) when compared with placebo. Indirect comparison analyses also showed denosumab to be consistently superior to oral bisphosphonates (alendronate and risedronate) in preventing new vertebral fractures, but comparisons with other active agents including zoledronic acid were inconsistent or non-statistically significant.

3.3 The Committee also noted that in men, the ADAMO trial showed an increase in bone mineral density and a reduction in bone turnover markers at 12 and 24 months following use with denosumab, but no reduction in risk of fractures was shown.

3.4 Clinical evidence for denosumab as second-line therapy after oral bisphosphonates was also considered by the Committee. Miller (2016) showed that denosumab was superior to zoledronic acid in improving bone mineral density and decreasing bone turnover markers in women who had received oral bisphosphonates for at least 2 years immediately before screening. The study did not however assess fracture as an outcome. In terms of safety, there were no cases of hypocalcaemia, fracture healing complications or osteonecrosis of the jaw reported in either treatment arm, but a lower incidence of musculoskeletal pain was shown in the denosumab arm.
Cost effectiveness

4.1 The Committee considered the cost-effectiveness of denosumab based on published studies, and noted that there were no local economic evaluations available. It acknowledged that published economic evidence from the UK showed that denosumab was considered to be cost effective for postmenopausal women at increased risk of fractures and for whom oral bisphosphonates were unsuitable, with ICERs ranging from dominant to \( <\£18,000/\text{QALY} \) when compared with no treatment or strontium ranelate.

4.2 The Committee concluded that at the price proposed by the manufacturer, denosumab was likely to be cost effective in Singapore if its use was restricted to patients who are unable to receive oral bisphosphonates.

Estimated annual technology cost

5.1 The Committee estimated that around 825 people in Singapore would benefit from Government assistance for denosumab. The annual cost impact was estimated to be less than \$1 million in the first years of listing on the MAF if treatment was restricted to postmenopausal women at increased risk of fractures and for whom oral bisphosphonates were unsuitable.

Additional considerations

6.1 The Committee heard that there was a potential increase in risk of severe hypocalcaemia with denosumab use in patients with chronic kidney disease of stage 3 and above. The Committee was aware that hypocalcaemia may occur at any time point within the 6 months after denosumab has been administered due to its long duration of action. In light of these concerns, the Committee agreed that subsidy for denosumab should be restricted to patients with sufficient renal function (that is, renal function eGFR > 30ml/min).
Recommendation

7.1 The Committee recommended denosumab 60mg pre-filled syringe for listing on the MAF for the treatment of osteoporosis in post-menopausal women at high risk of fracture who meet certain clinical conditions, on the basis of its superior reduction in fractures compared with placebo and acceptable cost-effectiveness at the price proposed by the manufacturer compared with zoledronic acid.

7.2 Denosumab was not recommended for subsidy for men with osteoporosis due to the lack of available clinical and economic evidence supporting its use in this patient group.

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.

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