Technology Guidance

Denosumab

for treating osteoporosis and glucocorticoid-associated bone loss

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

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

- ✓ Denosumab 60 mg/mL prefilled syringe for treating patients with osteoporosis (T-score ≤ -2.5) at high risk of fracture.

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

Subsidy status

Denosumab 60 mg/mL prefilled syringe is recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indication with effect from 1 July 2022.

MAF assistance **does not** apply to denosumab 60 mg/mL prefilled syringe when used for treating glucocorticoid-associated bone loss.

Updated: 1 July 2022

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 treating men and postmenopausal women with osteoporosis at high risk of fracture in November 2016. The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical experts from the public healthcare institutions. Published clinical and economic evidence on the use of denosumab as an initial treatment for osteoporosis was considered, 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; 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 subsidy considerations.

1.4. In March 2022, the Committee considered a request from the public healthcare institutions to expand the MAF listing for denosumab to allow use in men with osteoporosis and enable more women with osteoporosis to access subsidised treatment (i.e., to not restrict subsidy to women who have eGFR > 30 mL/min and who are unable to tolerate or follow the administration instructions for oral bisphosphonates). The Committee also considered evidence for a new indication approved by the Health Sciences Authority (HSA) for denosumab for treating glucocorticoid-associated bone loss.

Clinical need

2.1. In November 2016, the Committee heard that denosumab was considered by local clinicians as the preferred treatment for osteoporosis in both men and postmenopausal women, after oral bisphosphonates. Only patients who have renal impairment, expected gastrointestinal intolerance to bisphosphonates or contraindication to bisphosphonates receive denosumab as initial therapy due to its high cost compared with generic oral bisphosphonates.

2.2. In March 2022, the Committee recalled that denosumab was listed on the MAF in 2017 for treating postmenopausal women with osteoporosis (T-score ≤ -2.5) who have a high risk of fracture and eGFR > 30 mL/min, and who are unable to tolerate or follow the administration instructions for oral bisphosphonates.

2.3. The Committee heard that since the subsidy listing for denosumab was implemented, there is also a role for denosumab as an initial treatment over bisphosphonates in certain patients who have markedly low bone density, very high risk of fracture, or renal impairment (eGFR ≤ 30 mL/min), in line with international clinical practice guidelines. In addition, denosumab is also used in local practice as subsequent therapy in women who have had an inadequate response to, or have already received several years of treatment with, oral bisphosphonates.

2.4. Local clinicians confirmed that the same treatment approach for osteoporosis is applied for men as no differences in treatment response are expected. Denosumab is also reimbursed in most overseas reference jurisdictions for both men and women with osteoporosis. The Committee recalled that denosumab was previously not recommended for subsidy for treating men with osteoporosis, but agreed to reconsider expanding the MAF listing in view of the clinical need to provide subsidised treatment for men with osteoporosis.

2.5. The Committee noted that international clinical guidelines recommend oral bisphosphonates as the preferred treatment for glucocorticoid-associated bone loss due to favourable safety and cost, while zoledronic acid, teriparatide and denosumab are alternative options when the use of oral bisphosphonates is contraindicated or inappropriate. Given that alendronate, risedronate and zoledronic acid are already subsidised and used in local practice, and denosumab is not reimbursed in any overseas reference jurisdictions for treating glucocorticoid-associated bone loss, the Committee considered that there was limited clinical need to consider denosumab for subsidy for this indication.

2.6. The Committee heard that the local prevalence of osteoporosis and glucocorticoid-associated bone loss could not be accurately determined due to the lack of epidemiological data. Based on local clinician estimates, they noted that postmenopausal women were likely to comprise the majority of patients who require treatment for osteoporosis, followed by men with osteoporosis, and patients with glucocorticoid-induced osteoporosis.

Clinical effectiveness and safety

3.1. In November 2016, the Committee agreed that intravenous zoledronic acid, which was listed on the MAF at the time of the evaluation, was the appropriate comparator for denosumab for treating osteoporosis.

3.2. The Committee noted that there were no head-to-head trials comparing denosumab with zoledronic acid as initial 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. Clinical evidence for denosumab as subsequent 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.

3.4. 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. In March 2022, the Committee noted from international clinical guidelines that there was no evidence to show that skeletal metabolism differs fundamentally between men and women. Therefore, the Committee considered that it was plausible for men with osteoporosis to derive similar clinical benefits (e.g., in reducing the risk of fractures) from denosumab treatment as postmenopausal women with osteoporosis.

3.5. In March 2022, the Committee also reviewed the available clinical evidence from a randomised controlled trial (Saag 2018 and 2019) on the use of denosumab in adults with glucocorticoid-associated bone loss. Results showed that denosumab was superior to risedronate in increasing bone mineral density at the lumbar spine and hip, but no reduction in the risk of fractures was shown. The Committee considered that the clinical benefit of denosumab treatment in postmenopausal osteoporosis could not be extrapolated to glucocorticoid-associated bone loss, as the pathophysiology of these conditions differed substantially. Hence, it was uncertain whether denosumab could provide clinically meaningful outcomes in patients with glucocorticoid-associated bone loss.

Cost effectiveness

4.1. In November 2016, the Committee considered the cost-effectiveness of denosumab for treating osteoporosis 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 with osteoporosis at increased risk of fractures and for whom oral bisphosphonates were unsuitable, with ICERs ranging from dominant to <£18,000/QALY when compared with no treatment or strontium ranelate. The Committee concluded that at the price proposed by the manufacturer, denosumab was likely to be cost effective in Singapore for treating osteoporosis if its use was restricted to patients who are unable to receive oral bisphosphonates.

4.2. In March 2022, the Committee considered a revised pricing proposal for denosumab from the manufacturer and acknowledged that the proposed price was comparable to prices in overseas reference jurisdictions that already fund denosumab for women and men with osteoporosis. Thus, the Committee agreed that denosumab was likely to represent an acceptable use of healthcare resources in Singapore for treating both women and men with osteoporosis who are at high risk of fracture.

4.3. No local economic evaluations on the use of denosumab for glucocorticoid-associated bone loss were identified. The Committee noted that none of the overseas reference HTA agencies had reviewed denosumab for this indication.

Estimated annual technology cost

5.1. In November 2016, the Committee estimated that the annual cost impact was less than SG$1 million in the first year of listing denosumab on the MAF if treatment was restricted to postmenopausal women at increased risk of fractures and for whom oral bisphosphonates were unsuitable.

5.2. In March 2022, the Committee estimated that an additional annual cost of between SG$1 million to less than SG$3 million was required if the MAF listing of denosumab was expanded to include men and women with osteoporosis at high risk of fracture (without restricting to those who have eGFR > 30 mL/min and who are unable to tolerate or follow the administration instructions for oral bisphosphonates).

5.3. The Committee acknowledged that the cost impact of listing denosumab on the MAF for treating glucocorticoid-associated bone loss was uncertain, since glucocorticoids are used in many chronic conditions and the target population requiring treatment for bone loss could include young adults.

Additional considerations

6.1. In November 2016, the Committee heard from local clinicians 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 > 30 mL/min).

6.2. In March 2022, the Committee reassessed the use of denosumab for treating osteoporosis in patients with severe renal impairment, and noted that denosumab was the only treatment option in this group of patients. In view of the clinical need, the Committee considered that the existing MAF clinical criteria for denosumab should be relaxed to allow clinicians to exercise professional judgment when choosing treatments for patients with severe renal impairment.

Recommendations

7.1. In November 2016, the Committee recommended denosumab 60 mg/mL prefilled syringe for listing on the MAF for treating osteoporosis (T-score ≤ -2.5) in post-menopausal women at high risk of fracture who have eGFR > 30 mL/min and are unable to tolerate or follow the administration instructions for oral bisphosphonates, 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. 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 at the time of the evaluation.

7.2. In March 2022, the Committee recommended an expansion of the MAF listing for denosumab to include men and women with osteoporosis (T-score ≤ -2.5) at high risk of fracture, in view of the clinical need for effective treatment options and favourable cost-effectiveness at the revised price proposed by the manufacturer.

7.3. The Committee did not recommend denosumab for listing on MAF for treating glucocorticoid-associated bone loss, due to limited clinical need, uncertain clinical benefit, and uncertain budget impact.

VERSION HISTORY

Guidance on denosumab for treating osteoporosis and glucocorticoid-associated bone loss

This Version History is provided to track any updates or changes to the guidance following the first publication date. It is not part of the guidance.

1. **Publication of guidance**

   Date of Publication 3 May 2017

2. **Guidance updated to include a review of denosumab for a wider population of women with osteoporosis, men with osteoporosis, and patients with glucocorticoid-associated bone loss**

   Date of Publication 1 July 2022

About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

As the national HTA agency, ACE conducts evaluations to inform government subsidy decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

This guidance is based on the evidence available to the MOH Drug Advisory Committee as at 25 November 2016 and 18 March 2022. It is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

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Chief HTA Officer
Agency for Care Effectiveness
Email: ACE_HTA@moh.gov.sg