Technology Guidance

Romosozumab and teriparatide

for treating osteoporosis

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has not recommended:

- Romosozumab or teriparatide for inclusion on the MOH List of Subsidised Drugs for treating postmenopausal women with osteoporosis who are at high risk for fracture; and
- Teriparatide for inclusion on the MOH List of Subsidised Drugs for treating men with primary or hypogonadal osteoporosis who are at high risk for fracture, or patients with glucocorticoid-induced osteoporosis who are at high risk for fracture

due to uncertain extent of clinical benefit and unfavourable cost-effectiveness compared with subsidised alternatives.

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Factors considered to inform the recommendations for funding

Technology evaluation

1.1. The MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of romosozumab and teriparatide for treating osteoporosis in various patient groups. The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical and patient experts from public healthcare institutions and local patient and voluntary organisations, respectively. Published clinical and economic evidence for romosozumab and teriparatide was considered in line with their registered indications.

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. In local clinical practice, drug treatments for osteoporosis include antiresorptive and anabolic agents. Several antiresorptive agents (alendronate, denosumab, risedronate and zoledronic acid) are included in the MOH List of Subsidised Drugs, but anabolic agents (romosozumab and teriparatide) are currently not subsidised.

2.2. The Committee heard that both romosozumab and teriparatide are approved by HSA for treating postmenopausal women with osteoporosis who are at high risk for fracture. Teriparatide is additionally approved for treating men with primary or hypogonadal osteoporosis who are at high risk for fracture, as well as patients with glucocorticoid-induced osteoporosis who are at high risk for fracture.

2.3. For postmenopausal osteoporosis, the Committee noted that international clinical guidelines recommend stratifying patients by level of fracture risk to inform the selection of initial treatment. For women with high fracture risk, oral bisphosphonates such as alendronate and risedronate are widely used as initial treatment in local practice. Denosumab, romosozumab, teriparatide and zoledronic acid are considered for patients who are unable to receive or have an inadequate response to oral bisphosphonates. For women with very high fracture risk, some clinicians prefer using romosozumab or teriparatide as initial treatment, although denosumab and zoledronic acid are still commonly prescribed.

2.4. The Committee heard that locally, men with osteoporosis are treated with the same approach used for postmenopausal women with osteoporosis, because no differences in treatment response are expected between these patient groups.

2.5. For glucocorticoid-induced osteoporosis, the Committee noted that international guidelines recommend oral bisphosphonates as the preferred treatment. Zoledronic acid, teriparatide and denosumab may be considered as alternative treatment options.

2.6. The Committee considered testimonials from local patient experts about living with osteoporosis and their experience with different treatments. The Committee heard that most patients who provided input into the evaluation were receiving treatment with denosumab and felt that it was effective, well tolerated, and convenient to administer every six months. The Committee noted that a patient previously treated with teriparatide experienced some initial side effects that resolved spontaneously, but their bone mineral density (BMD) did not improve after two years of treatment. The patient also explained that teriparatide was inconvenient to use while travelling as it requires refrigeration, and the daily injections required extra care to rotate injection sites to prevent skin bruising. Most patients were not familiar with romosozumab and considered that any new treatments for osteoporosis should improve BMD and be more affordable than their current treatment.

Clinical effectiveness and safety

3.1. Postmenopausal women with osteoporosis

The Committee reviewed the clinical evidence from randomised controlled trials (RCTs) of romosozumab and teriparatide in postmenopausal women with osteoporosis. In phase III trials (ARCH and VERO), romosozumab and teriparatide were superior to oral bisphosphonates (alendronate or risedronate) in reducing the risk of new fractures. However, the Committee noted that there were no phase III trials comparing the anabolic agents with denosumab or zoledronic acid, which were the relevant comparators for this evaluation.

3.2. The Committee heard that a small phase II RCT (DATA) showed no significant differences between teriparatide and denosumab in terms of BMD increase in the lumbar spine, femoral neck and total hip after 24 months of treatment. The trial was not powered to detect any changes in fracture rates. The Committee also reviewed results from the extension study (DATA-Switch), where patients who switched from teriparatide to denosumab treatment showed further BMD increase, and patients who switched from denosumab to teriparatide treatment showed transient or progressive BMD loss. While the results suggested that the order denosumab and teriparatide are used has an impact on overall treatment efficacy in postmenopausal osteoporosis, the Committee considered the study had several limitations including small sample size, and lack of fracture outcomes to assess the clinical impact of the BMD changes.

3.3. In the absence of direct comparative evidence between romosozumab and denosumab or zoledronic acid, the Committee considered the results of indirect treatment comparisons that were reviewed by CADTH (Canada) and NICE (UK). While acknowledging the uncertainty associated with indirect comparisons due to the heterogeneity of trial populations, the Committee noted that no significant differences were evident between romosozumab and either denosumab or zoledronic acid in reducing the risk of fractures. No relevant indirect comparison between teriparatide and denosumab or zoledronic acid was identified.

3.4. Between romosozumab and teriparatide, results from a phase III RCT (STRUCTURE) showed that romosozumab led to greater gains in BMD in the lumbar spine, femoral neck and total hip compared with teriparatide after 12 months of treatment. However, the study was not powered to assess any differences in fracture incidence between treatments.

3.5. The Committee noted that PBAC (Australia) reviewed an indirect treatment comparison between romosozumab and teriparatide that was informed by data from placebo-controlled trials. While the analyses were associated with uncertainty, the results suggested there were no significant differences in fracture outcomes between the two agents. The Committee also heard that local clinicians considered the clinical effectiveness of romosozumab and teriparatide were likely to be comparable.

3.6. In terms of safety, the ARCH trial reported more cases of serious cardiovascular adverse events such as cardiac ischemic events and cerebrovascular events observed with romosozumab compared with alendronate. In the VERO trial, there were more cases of pain in the extremities, dizziness and hypercalcaemia reported with teriparatide compared with risedronate.

3.7. Overall, based on available evidence and given the absence of head-to-head confirmatory trials with fracture-reduction endpoints, the Committee considered that the extent of clinical benefit provided by romosozumab and teriparatide compared with denosumab or zoledronic acid was uncertain for postmenopausal women with osteoporosis.

3.8. Men with primary or hypogonadal osteoporosis

The Committee heard the available clinical evidence supporting the use of teriparatide in men with osteoporosis was limited to a placebo-controlled trial, and they acknowledged that the comparative benefit of teriparatide relative to denosumab or zoledronic acid remained uncertain in this population.

3.9. Patients with glucocorticoid-induced osteoporosis

The Committee reviewed clinical evidence from a phase III RCT (Saag 2007 and 2009) involving adults with glucocorticoid-induced osteoporosis that showed teriparatide treatment led to greater improvements in BMD compared with alendronate. However, the study lacked statistical power to assess fracture outcomes. Apart from alendronate, teriparatide has not been compared with other alternative agents in RCTs, and no relevant indirect comparisons have been reviewed by overseas HTA agencies.

3.10. Overall, the Committee considered that in this population, the extent of clinical benefit provided by teriparatide was uncertain compared with subsidised alternatives such as alendronate, risedronate and zoledronic acid.

Cost effectiveness

4.1. The companies of romosozumab and teriparatide were invited to submit value-based pricing proposals for their products for funding consideration in line with the HSA-approved indications.

4.2. For the treatment of osteoporosis in postmenopausal women and in men, the Committee noted there were no relevant cost-effectiveness studies published locally or from overseas HTA agencies comparing romosozumab or teriparatide with denosumab or zoledronic acid. The Committee also heard that romosozumab was compared with teriparatide via a cost-minimisation analysis in PBAC's evaluation.

4.3. For the treatment of glucocorticoid-induced osteoporosis, the Committee reviewed the evaluations from CADTH and PBAC that indicated teriparatide was not considered cost-effective compared with alendronate. No local or overseas economic evaluations comparing teriparatide with other treatment alternatives were identified.

4.4. The Committee acknowledged that the annual treatment costs with romosozumab and teriparatide remained substantially higher compared with subsidised alternatives. Given the uncertain comparative clinical benefit, the Committee considered that romosozumab and teriparatide were unlikely to represent a cost-effective use of healthcare resources at current prices.

Estimated annual technology cost

5.1. The Committee noted that the annual cost impact to the public healthcare system was estimated to be less than SG$1 million for romosozumab, or between SG$1 million to less than SG$3 million for teriparatide, in the first year of listing on the MOH List of Subsidised Drugs for treating postmenopausal women with osteoporosis.

5.2. The annual cost impact in the first year of listing teriparatide on the MOH List of Subsidised Drugs for treating men with primary or hypogonadal osteoporosis and patients with glucocorticoid-induced osteoporosis was estimated to be less than SG$1 million for each patient group.

Recommendations

6.1. Based on available evidence, the Committee recommended not listing romosozumab and teriparatide on the MOH List of Subsidised Drugs for treating postmenopausal women with osteoporosis who are at high risk for fracture due to the uncertain extent of clinical benefit and unfavourable cost-effectiveness compared with alternative treatments.

6.2. The Committee also recommended not listing teriparatide on the MOH List of Subsidised Drugs for treating men with primary or hypogonadal osteoporosis who are at high risk for fracture, or patients with glucocorticoid-induced osteoporosis who are at high risk for fracture, due to the uncertain extent of clinical benefit and unfavourable cost-effectiveness compared with alternative treatments.

Agency for Care Effectiveness - ACE Agency for Care Effectiveness (ACE)

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 funding 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 7 March 2023. 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.

Find out more about ACE at www.ace-hta.gov.sg/about

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