**Title Page:**

**Denosumab for the treatment of osteoporosis**

**(Therapeutic Brief)**

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Running Title:

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**Abstract:**

Denosumab is a monoclonal antibody which binds to the receptor activator of nuclear factor-κB ligand (RANKL), reducing osteoclastic activity and bone turnover. The Fracture REduction Evaulation of Denosumab in Osteoporosis every 6 Months (FREEDOM) trial showed a significant reduction in relative risk of fractures with increased bone mineral density (BMD) with denosumab. A trial of DenosumAb versus placebo in Males with Osteoporosis (ADAMO) demonstrated the similar effect of denosumab for improving BMD and reducing bone turnover in men. However, recently concerns were identified regarding increased risk of fractures with denosumab cessation. Until further evidence is available, bisphosphonate treatment is recommended to attenuate this risk with denosumab discontinuation.

**Key Words:**

denosumab; fractures; osteoporosis

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Denosumab is a fully human monoclonal antibody used for osteoporosis treatment. It has a high affinity and specificity for the receptor activator of nuclear factor-κB ligand (RANKL), a cytokine and mediator of osteoclastic bone resorption. Denosumab inhibits RANKL, resulting in reduced differentiation, activity and survival of osteoclasts, causing reduced bone resorption [1]. Although it is administered as a subcutaneous injection every six months, the Denosumab Adherence Preference Satisfaction (DAPS) study showed that 92.4% preferred denosumab over oral alendronate, with associated compliance and satisfaction rates [2].

The landmark trial confirming its benefit in osteoporosis treatment was the Fracture REduction Evaulation of Denosumab in Osteoporosis every 6 Months (FREEDOM) trial. 7808 osteoporotic older women were randomised to denosumab or placebo for 36 months. Denosumab was associated with relative risk reductions of new radiographic vertebral fractures (68%), non-vertebral fractures (20%) and hip fractures (40%) [3]. The extension of the FREEDOM study showed the benefits of denosumab treatment continued for up to ten years in terms of low fracture incidence and increased BMD without plateau, with low rates of adverse events [4]. However, subgroup analyses showed the risk reduction was significant only in women with a baseline femoral neck bone mineral density (BMD) T‐score ≤ −2.5, body mass index (BMI) < below 25 kg/m2 and in those without a prevalent vertebral fracture [5].

The FREEDOM study also showed that denosumab was associated with reductions in serum C‐telopeptide of type I collagen (CTX), a biochemical marker of bone resorption, to below premenopausal reference intervals [6]. There were also improvements in hip and spine strength by 14.3% and 22.4% at 36 months compared to placebo, measured through nonlinear finite element analysis (FEA) of hip and spine quantitative computed tomography (QCT) scans [7]. The increased hip and spine strength was seen in both the trabecular and cortical bone components.

The benefits of denosumab was also demonstrated in men with low BMD in A trial of DenosumAb versus placebo in Males with Osteoporosis (ADAMO). When 228 men were randomised to denosumab or placebo for 24 months, treatment was associated with increased BMD and reduced bone resorption at levels similar to the FREEDOM study [8].

A case series of severe spontaneous vertebral fractures after denosumab discontinuation raised concerns regarding severe osteoporosis rebound with treatment cessation [9]. An observational study found a reversal of BMD benefits and possibly fracture risk, identifying eight (9.8%) patients who experienced 17 fractures within the year [10]. When the FREEDOM study participants who discontinued denosumab were followed-up for up to 24 months, there were similar fracture rates in the denosumab (7%) and placebo (9%) groups, without any differences in fracture occurrence patterns [11]. However, until further evidence is available, it is recommended to assess the risk and benefit of denosumab treatment after five years, and to consider bisphosphonates if denosumab was discontinued to attenuate rebound increases in bone turnover [12].

In summary, denosumab is useful for osteoporosis management, but clinicians should be aware of increased fracture risk with treatment discontinuation.

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