

# NEW DRUG EVALUATION

No. 105

June 2010

## DENOSUMAB<sup>▼</sup> FOR POSTMENOPAUSAL OSTEOPOROSIS

Denosumab is a monoclonal antibody administered twice yearly by sub-cutaneous injection for the treatment of postmenopausal osteoporosis (PMO) in women at increased risk of fractures. Denosumab has been shown to reduce the risk of new vertebral fractures when compared to placebo and to improve BMD to a greater extent than alendronate or placebo. Frequency of adverse events appears similar to that of alendronate, but long term safety data are lacking. Denosumab is considerably more expensive than oral bisphosphonates, but it is comparable in cost to other agents used for the treatment of PMO when bisphosphonates are unsuitable. Denosumab, in line with preliminary NICE guidance, should be considered as a treatment option for the primary prevention of PMO only in women at increased risk of fractures for whom oral bisphosphonates are unsuitable.

### What is it?

Denosumab (Prolia<sup>▼</sup>, Amgen) is a human monoclonal antibody which inhibits the receptor activator of nuclear factor- $\kappa$ -B ligand (RANKL).<sup>1,2</sup> It is indicated for the treatment of postmenopausal osteoporosis (PMO) in women at increased risk of fracture, at a dose of 60 mg administered by single subcutaneous (sc) injection once every six months. Patients receiving denosumab must be supplemented sufficiently with calcium and vitamin D.<sup>2</sup> PMO is defined by a BMD score which is 2.5 standard deviations below the mean for young, adult, Caucasian women (T-score  $\leq$  -2.5).<sup>3</sup> Denosumab is also licensed for the treatment of bone loss in men associated with hormone ablation therapy for prostate cancer (not covered in this evaluation).

### How effective is it?

Four randomised phase III trials have evaluated the efficacy of denosumab 60 mg sc given every six months in postmenopausal women. Only one compared fractures rates, with the others reporting surrogate outcomes such as change in BMD as the primary endpoint.

The FREEDOM study compared the fracture rates in 7,868 women with PMO who were randomised to receive denosumab or placebo every six months, for 36 months. Denosumab treatment significantly reduced the incidence of new radiographic vertebral fractures at 36 months vs. placebo (2.3% vs. 7.2%; absolute risk reduction (ARR) = 4.9%; number needed to treat (NNT) = 21; hazard ratio (HR): 0.32 [95% confidence interval [CI]: 0.26 to 0.41];  $p < 0.001$ ). Risk of hip fractures was also significantly reduced (0.7% vs. 1.2%; unadjusted ARR = 0.5%; NNT = 200; HR: 0.60 [95% CI: 0.37 to 0.97];  $p = 0.04$ ).<sup>4</sup>

The DEFEND study (n = 332) compared the effect of denosumab and placebo on BMD in PM women with a T-score between -1 and -2.5 (osteopenia) over two

years. Denosumab treatment significantly increased BMD at all measured skeletal sites compared with placebo ( $p < 0.0001$ ).<sup>3</sup>

The DECIDE study compared the efficacy of denosumab and alendronate therapy (70 mg weekly) in 1,189 PM women with a T-score  $\leq$  -2. At 12 months, patients receiving denosumab had greater BMD gains than those receiving alendronate, at all measured sites. The mean hip BMD increase (primary endpoint) was +3.5% vs. +2.6% (absolute difference = 1.0% [95% CI: 0.7 to 1.2], NNT = 100,  $p < 0.0001$ ).<sup>5</sup>

The double-blind STAND study conducted in women previously treated with alendronate compared the effects of switching to denosumab on BMD, with continued alendronate therapy. Following a one month run-in period in which patients received alendronate once weekly, 504 PM women with T-scores of -2.0 to -4.0 at the lumbar spine or total hip were randomised to receive sc denosumab or continue therapy with alendronate (70 mg once weekly). In patients switching to denosumab, total hip BMD increased by 1.9% vs. 1.05% in those continuing on alendronate after 12 months (absolute difference = 0.85% [95% CI 0.44% - 1.25%], NNT = 118,  $p < 0.0001$ ); the lower limit of the CI excluded the prespecified noninferiority margin (-0.35%), thus showing the noninferiority of denosumab compared with alendronate.<sup>1</sup>

### How safe is it?

No statistically significant differences in the frequency of adverse events (AEs) among those receiving denosumab, placebo, or alendronate have been reported. In the pivotal FREEDOM study the most common AEs reported in both the denosumab and placebo groups were arthralgia, nasopharyngitis, back pain, and headache. Cellulitis occurred more frequently with denosumab (0.3% vs.  $< 0.1\%$ ,  $p = 0.002$ ). No cases of osteonecrosis of the jaw were reported.

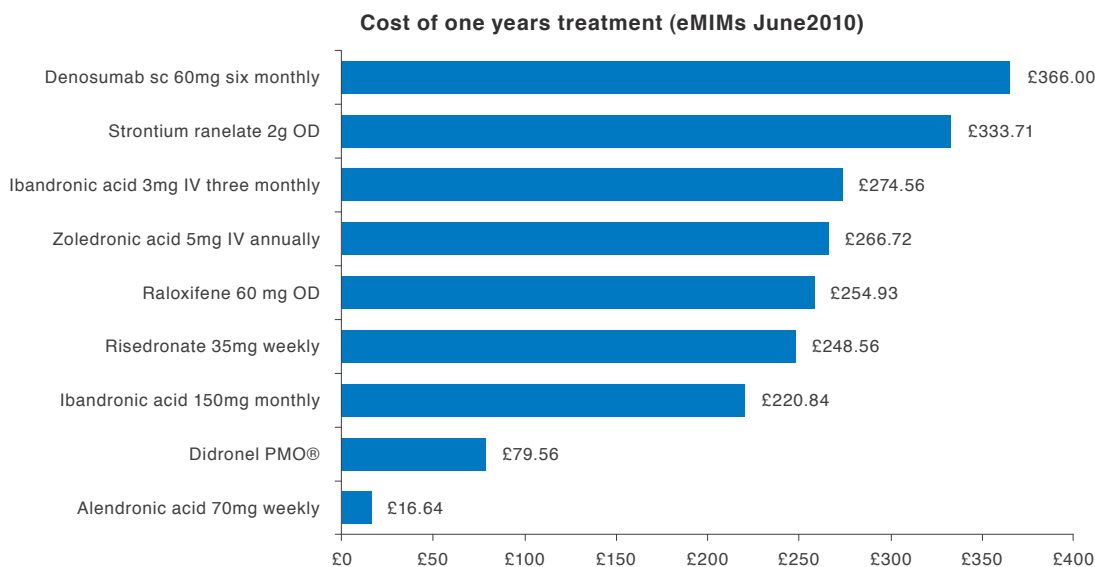
Concerns have been expressed by the FDA about the long term safety of the drug, especially the possible effects of inhibition of RANKL on the immune system and the risk of cancer or infections.<sup>6</sup> In a pooled safety analysis of the FREEDOM and DEFEND studies the FDA reported an absolute difference in malignant or unspecified neoplasm's of 0.5%. However, a statistically significant increase in the overall incidence of cancer or infections was not reported in any of the above studies. Additional data are needed to establish long-term safety.

'All suspected adverse reactions to black triangle drugs such as denosumab should be reported to the MHRA via the Yellow Card Scheme ([www.yellowcard.gov.uk](http://www.yellowcard.gov.uk)).'

### What other options are there?

NICE recommends alendronate as the first-line agent of choice for both primary and secondary prevention of osteoporotic fragility fractures in PM women, with risedronate and etidronate being alternative drugs for patients unable to comply with the special instructions for the administration of alendronate.<sup>7</sup> Strontium ranelate is considered to be a third-line option in those unsuitable for the first two drugs. Raloxifene and teriparatide are

### How much does it cost?



N.B. Doses shown are for general comparison only and do not imply therapeutic equivalence

## REFERENCES

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KEY RCT – randomised controlled trial, G – Guideline

**Regional Drug and Therapeutics Centre**  
**Wolfson Unit, Claremont Place, Newcastle upon Tyne NE2 4HH**  
**Tel: 0191 260 6188 Fax: 0191 260 6191**  
**Email: [nyrdtc.rxsupp@nuth.nhs.uk](mailto:nyrdtc.rxsupp@nuth.nhs.uk) Website: [www.nyrdtc.nhs.uk](http://www.nyrdtc.nhs.uk)**