Osteoporosis is a progressive skeletal disease in which low bone mass and deterioration of the micro-architecture of the bone leads to increased bone fragility and risk of fracture. There is an established link between fractures and morbidity, mortality and increased healthcare costs. According to the National Osteoporosis Society, one in two women and one in five men over the age of 50 in the UK will suffer from an osteoporotic fracture, with an estimated annual cost to the NHS of £2.3bn.

Currently available treatments to protect bones and reduce fracture risk include the bisphosphonates, strontium ranelate and hormonal treatments (eg, the selective oestrogen receptor modulator raloxifene). These treatments have proven efficacy (this is particularly true for the bisphosphonates), but they are not without problems. There is evidence to suggest that, despite their availability and proven effectiveness, as many as six in 10 patients do not adhere with treatment as prescribed after one year.

Denosumab

Denosumab is a fully human monoclonal antibody to receptor activator of NF-κB ligand (RANKL), which is a cytokine that modulates bone resorption through the osteoclastic receptor NF-κB. RANKL is an activator of osteoclastogenesis and osteoclast activity, and is inhibited by the ligand osteoprotegerin. There have been positive effects (eg, increased bone mineral density) after osteoprotegerin was administered experimentally to postmenopausal women. Because of concerns around the development of antibodies to osteoprotegerin, denosumab was developed as a therapeutic alternative.

Clinical evidence

The pivotal studies for denosumab were FREEDOM, DEFEND, DECIDE and STAND. Only FREEDOM was designed to assess fracture risk. The primary endpoint of FREEDOM was new radiographic vertebral fractures and secondary endpoints were time to non-vertebral fracture and time to first hip fracture. Over 36 months, new vertebral fractures occurred in 2.3% of 3,902 patients in the denosumab group compared with 7.2% of 3,906 patients in the placebo group (absolute risk reduction [ARR] 4.8%; P<0.001; number needed to treat [NNT] to prevent one fracture over 36 months = 20).

Non-vertebral fractures occurred in 6.5% of patients in the denosumab group compared with 8.0% of the control group (ARR 1.5%; P=0.01). Hip fractures occurred in 0.7% and 1.2% of the denosumab and placebo groups, respectively (ARR 0.5%; P=0.04).

The DEFEND trial compared the effect of denosumab on bone mineral density (BMD) with that of placebo in women with T-scores between –1 and –2.5 (a T-score is the difference between a patient's BMD and that of a healthy young woman, expressed as the number of standard deviations below the mean). The primary endpoint, change in T-score from baseline in the lumbar spine after two years, was +6.5% for...
Denosumab after treatment with alendronate

In DECFREEDOM, denosumab was compared with alendronate, with total hip BMD as the primary outcome measure.\(^2\) Total hip BMD increased by 3.5% in the denosumab group and by 2.6% in the alendronate group (ARR 1%; \(P<0.0001\); NNT=100). This study was not powered to compare fracture rates.

*Kendler et al* investigated the use of denosumab after treatment with alendronate in the STAND study.\(^3\) Women took alendronate 70mg weekly for a run-in period of one month and were then randomised to receive either denosumab or alendronate (with matching placebo). The primary hypothesis was that denosumab was non-inferior to alendronate and the primary endpoint was the percentage change in total hip BMD at 12 months. BMD was increased by 1.9% for denosumab versus 1.05% for those continuing on alendronate (\(P<0.0001\) for non-inferiority). Again, this study was not powered to compare fracture rates.

**Safety**

There were no significant differences in the overall number of adverse events reported by patients receiving denosumab compared with placebo in FREEDOM.\(^4\)

However, more frequently reported in the denosumab group were cellulitis (0.3% vs <0.1%) and eczema (3% vs 1.7%), but these differences were not statistically significant. Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis (acute onset of red, painful, hot, swollen and tender skin — usually affecting a single limb; this can be accompanied by malaise, shivering, nausea or rigors).

Other adverse effects identified from the main studies\(^5\) were arthralgia, back pain, constipation and nasopharyngitis, but these were not significantly different from the control groups.

The US Food and Drug Administration expressed concerns about the long-term safety of denosumab on the immune system due to inhibition of RANKL. However, a pooled safety analysis of FREEDOM\(^\text{TM}\) and DEFEND\(^\text{TM}\) found no significant differences in the incidences of cancer or infection between the denosumab and placebo groups.

No cases of osteonecrosis of the jaw were reported in the previously mentioned studies. But, it has been reported in other clinical studies (mainly in people with cancer) and is therefore listed as a possible adverse reaction in the summary of product characteristics.\(^6\)

Other common adverse events associated with denosumab include urinary tract infection, upper respiratory tract infection, sciatia, cataracts, constipation, rash, pain in extremities and skin infections (predominantly cellulitis).\(^7\)

**Place in therapy**

Denosumab is licensed for the treatment of:

- Osteoporosis in postmenopausal women at increased risk of fractures
- Bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures

Generic alendronate remains the first choice for prevention of fractures due to its lower cost (£16.64 per year).

The National Institute for Health and Clinical Excellence has recently issued a technology appraisal for denosumab for the prevention of osteoporotic fractures in postmenopausal women. The appraisal recommends denosumab for the primary and secondary prevention of osteoporotic fragility fractures in those who are at increased risk of fracture and who are unable to comply with the special instructions for administering alendronate, risendronate or etidronate, or have an intolerance or contraindication to these treatments.\(^8\)

For primary prevention, additional criteria have been defined. Women must have a specified combination of T-score, age and number of independent clinical risk factors for fracture.\(^9\) The guidance defines independent clinical risk factors for fracture as: parental history of hip fracture; alcohol intake of four or more units per day; and rheumatoid arthritis.\(^9\) According to the guidance, a woman with no clinical risk factors would have to be 75 years of age or older and have a T-score of at least −4.0 (or be aged 70–74 years with a T-score of at least −4.5) before treatment with denosumab might be considered.

Despite this, NICE guidance states that if women are already taking denosumab (before the appraisal was published), they should be given the option of remaining on treatment.

Denosumab, at £366 annually, is more expensive than alendronate, but compares favourably with the yearly cost of existing treatments: strontium (£333), intravenous ibandronic acid (£274), intravenous zoledronic acid (£266), raloxifene (£254), risendronate (£248) and oral ibandronic acid (£220).\(^10\)

**Administration**

Denosumab is administered at a dose of 60mg by subcutaneous injection every six months.

Similar to other osteoporosis treatments, additional calcium and vitamin D is recommended if dietary intake cannot be assured. Pharmacists presented with prescriptions for denosumab should be aware that hypocalcaemia must be corrected before treatment is initiated. Patients with an increased risk of hypocalcaemia (eg, patients with severe
renal impairment or on dialysis) should have their calcium levels monitored while taking denosumab. No dose adjustment is necessary for those with renal impairment or for older patients.

As yet, there are no reported interactions with any other medicines.

One of the advantages of denosumab over other parenteral treatments (e.g., zoledronic acid) is that it is administered as a subcutaneous injection. Treatment can therefore be given in primary care or perhaps be provided from community pharmacies.

### Other applications

There is evidence that denosumab is of benefit for reducing bone loss associated with hormone ablation in men with prostate cancer. There was a significant increase in lumbar spine BMD in the denosumab group (3.6%) compared with placebo (a decrease of 1%) over 24 months.\(^9\) The SCORTEN 2007 score for patients with metastatic breast cancer is taken from a study performed in patients with metastatic breast cancer. A skeletal-related event was defined as pathological fracture, spinal cord compression, or radiation therapy or surgery to the bone.\(^10\)

### References


### Help with treatment of depression in epilepsy

**Q** UK Medicines Information summarises the evidence for this frequently asked question: **What is the most appropriate antidepressant to use for a patient with epilepsy?**

**A** The first consideration should always be to check the patient’s anticonvulsant regimen for potential drug-induced depression. The patient could benefit from changing the anticonvulsant to another medicine with a more favourable effect on mood rather than adding an antidepressant.

Although the risk of seizures with most antidepressants is low, a risk still exists and patients should be made aware of this when treatment is prescribed. The risk of seizures rises with increasing antidepressant doses. Selective serotonin reuptake inhibitors (SSRIs) are considered the first-line antidepressant option for patients with epilepsy. Published data do not support the recommendation of a specific SSRI, although fluoxetine is not the best choice because of its long half-life, a possibility greater incidence of seizures and a higher likelihood of drug interactions. Citalopram or sertraline could be considered better options due to their lower potential for interactions with anticonvulsants.

Moclobemide is a good alternative because it has minimal proconvulsive effects but, due to limited evidence, it should be reserved as a second choice.

Tricyclic antidepressants (TCAs) should be used cautiously with patients with epilepsy and reserved for patients who respond poorly to or are intolerant of other antidepressants. Where a TCA is needed, doxepin is the drug of choice.

Clinicians should be aware of the possibility of interactions between antidepressants and anticonvulsants and should monitor carefully patients with epilepsy who are prescribed antidepressants.

Introducing the antidepressant gradually, starting with a low dose and not exceeding the maximum recommended doses may reduce the risk of seizures occurring.

If seizures do occur, or if the frequency of seizures increases, the antidepressant should be discontinued.