MTRAC
Midlands Therapeutics Review and Advisory Committee

Commissioning Support Denosumab *(Prolia®)*

For the treatment of osteoporosis

Commissioning guidance:

Commissioners may wish to bear the following in mind when considering the commissioning of denosumab for the treatment of osteoporosis:

- The need to optimise adherence to long-term bisphosphonate treatment.
- Existing NICE guidance on the use of denosumab in the primary and secondary prevention of osteoporotic fragility fractures.
- Denosumab may be suitable for prescribing and administration in primary care under the terms of a Local Commissioning contract. When commissioning this service, the following points may be relevant:
  - The need to ensure that the patient is calcium and vitamin D replete before the injection is administered. (Given uncertainties over how/when to assess deficiency, organisations may wish to develop local guidance)
  - Initiation of treatment in secondary care before transfer to primary care. (The committee discussed the need for agreement regarding adequate follow-up of the first injection, especially given the potential risk of hypocalcaemia with denosumab treatment, and then agreement between specialist and GP regarding who will administer the second and subsequent injections)
  - The need for timely reminder/repeat appointment systems to ensure that the patient receives regular six-monthly injections, and any preceding tests.

MTRAC considered denosumab because it is a treatment with potential for use in primary care.

Description of technology

Denosumab is a human monoclonal antibody (IgG2), which inhibits osteoclast-mediated bone breakdown, thereby decreasing bone resorption in cortical and trabecular bone.

This guidance sheet relates to the use of denosumab for the treatment of osteoporosis in men and postmenopausal women at increased risk of fractures. The recommended dose is 60 mg administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or upper arm. Patients must be adequately supplemented with calcium and vitamin D.[2] For full details, please see the Summary of Product Characteristics (SPC).[1]

Background

Osteoporosis is a disease characterised by low bone mass and progressive deterioration of bone tissue leading to increased fragility and a consequent susceptibility to fracture. Risk factors for fragility fractures include: reduced bone mineral density (BMD), the use of oral or systemic glucocorticoids, age, sex, previous fractures and a family history of osteoporosis[2]. Due to increased bone loss with the menopause in women, and age-related bone loss in men and women, the prevalence of osteoporosis increases with age from 2% at 50 years to more than 25% at 80 years in women.[2] More than one-third of adult women, and one in five men will sustain one or more fragility fractures in their lifetime.[3]

Of the approximately 536,000 new fragility fractures occurring each year, 79,000 are hip fractures, and 66,000 clinically diagnosed vertebral fractures. About 53% of patients suffering a hip fracture can no longer live independently, and 28.7% die within 12 months of the fracture[3]. Furthermore, most major osteoporotic fractures are associated with reduced relative survival, with an impact persisting more than five years after the fracture.

NICE guidance on assessing the risk of fragility fracture recommends the use of FRAX or QFracture to assess the person's 10-year absolute risk of a fracture to inform further treatment steps. Guidance on denosumab (TA204) in postmenopausal women with osteoporosis recommends that for **primary prevention**, it is an option in women for whom alendronate or risedronate are unsuitable **and** who have an appropriate combination of T-score, age, and independent clinical risk factors for fracture (parental history of hip fracture, alcohol intake of 4 or more units per day, or rheumatoid arthritis). As **secondary prevention of osteoporosis**, it is recommended as a treatment option in women at increased risk of fractures if alendronate or risedronate are unsuitable.[4] The guidance is due to be updated as part of the a new review of non-bisphosphonates for the treatment of osteoporosis, currently in preparation.[5]

Clinical evidence for efficacy and safety

Trials selected for the MTRAC review focused on fracture incidence as the primary outcome, or change in BMD where fracture incidence was not a stated outcome.

In postmenopausal women with osteoporosis, the FREEDOM randomised controlled trial (RCT)[6] compared the incidence of fractures with denosumab treatment *vs*. placebo in 7,868 women aged 60 to 90 with osteoporosis and a BMD T-score less than -2.5 to -4.0 at the lumbar spine or total hip. All women received daily supplements of calcium (at least 1000 mg) and vitamin D (dose determined by baseline 25-hydroxyvitamin D concentration). Study participants received injections of 60 mg denosumab or placebo every six months for 36 months. The primary outcome

was the rate of new vertebral fractures imaged using lateral spine radiographs taken annually and assessed by a semi-quantitative grading scale. Secondary outcomes were the incidences of the first non-vertebral fracture and first hip fracture. BMD was evaluated using dual x-ray absorptiometry at baseline, annually at the hip and after 36 months at the lumbar spine. In a seven-year extension, all participants received 60 mg denosumab every six months, and safety and tolerability outcomes were measured[7].

Results: After 36 months' treatment, the incidence of new vertebral fractures was significantly lower with denosumab (2.3% [86/3,702 participants]) than placebo treatment (7.2% [264/3,691]); hazard ratio 0.32 (95% CI 0.26 to 0.41).[6] The absolute risk reduction between treatments was 4.8% (95% CI 3.9 to 5.8); number needed to treat (NNT) 21 over 36 months[8]. After ten years of treatment[7], the annualised incidence of new vertebral fractures ranged from 0.70 to 1.47% in the long-term treatment group (10 years of treatment), and from 0.9% to 1.86% in the crossover group (3 years placebo, then 7 years denosumab). These percentages did not vary significantly across the 10 years of data presented. The cumulative incidence of new vertebral fractures over years 4 to 10 was 7% in the long-term treatment group and 9.3% in the crossover group.

Secondary outcomes: significant reductions in clinically diagnosed vertebral fractures (0.8% for denosumab *vs.* 2.6%, $p < 0.001$) and hip fractures (0.7% *vs.* 1.2%, $p = 0.04$). After three years, BMD increased by 9.2% (95% CI 8.2 to 10.1) with denosumab at the lumbar spine and 6.0% (95% CI 5.2 to 6.7) at the total hip, as compared with minimal change or slight decreases observed with placebo. This elevation in BMD was maintained during the extension study.[7]

Denosumab treatment for ***osteoporosis or low BMD in men*** was evaluated in the ADAMO trial[9 10], a one-year placebo-controlled RCT that enrolled 242 men with osteoporosis or low BMD, followed by a one-year open-label extension where all participants received denosumab. Study participants received placebo or a denosumab 60 mg sc injection every six months. The primary outcome was change in BMD assessed using DXA scanning at the lumbar spine.

Results: Denosumab treatment increased mean lumbar spine BMD by 5.7% at month 12, compared with an increase of 0.9% with placebo. The difference between treatment groups was 4.8% ($p < 0.0001$; 95% CI 4.0 to 5.6%). BMD was also significantly increased at all other skeletal sites measured including the total hip, femoral neck, trochanter, and forearm ($p \leq 0.0144$ for all comparisons). During the 12-month extension phase, further increases in BMD were measured at all skeletal sites, bringing the cumulative gain at the lumbar spine, for example to 8%. Clinical fractures occurred in two (1.7%) and one (0.8%) participant in the placebo- and denosumab-treated groups, respectively, during the double-blind phase. During the open-label phase, two rib fractures in two men were classed as osteoporotic clinical fractures.

Adverse events (AE)

In the FREEDOM trial, there were no significant differences between denosumab or placebo for the incidences of AEs, serious AEs, or discontinuation of study treatment due to an AE. During the 10-year extension phase[7], there were nine hip or thigh fractures, two of which were considered atypical. There were also 13 confirmed cases of osteonecrosis of the jaw (ONJ): seven in the long-term group and six in the crossover group (5.2 per 10,000 participant-years)[7].

In male patients in the ADAMO trial, most AE were mild or moderate in severity; the most frequent (5% incidence) were back pain, arthralgia, nasopharyngitis, and constipation. There were no reports of hypocalcaemia, ONJ, fracture healing complications, or atypical femoral fracture[9 10] during the two-year study.

Medicines and Healthcare Regulatory Agency (MHRA) warnings related to denosumab include: monitoring required for severe symptomatic hypocalcaemia (2012), rare cases of atypical femoral fracture with long-term use (2013), further measures to decrease risk of ONJ (2015), and Osteonecrosis of the external auditory canal (2017).

Considerations for cost impact

- At current prices, the annual cost of denosumab 60 mg, given as a twice-yearly subcutaneous injection is £366. *[Price taken from MIMS, June 2019]*

References

1. Amgen. Summary of Product Characteristics. Prolia. *EMC* 2018.
2. CG146 Osteoporosis: assessing the risk of fragility fracture. *NICE* 2012. https://www.nice.org.uk/guidance/cg146.
3. NOGG 2017: Clinical guideline for the prevention and treatment of osteoporosis.
4. TA204 Denosumab for the prevention of osteoporotic fractures in postmenopausal women. *NICE* 2010.
5. NICE. Non-bisphosphonates for treating osteoporosis [ID901] 2019.
6. Cummings SR et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 2009;361(8):756-65
7. Bone HG et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. *Lancet Diabetes Endocrinol* 2017;5(7):513-23.
8. London New Drugs Group. APC/DTB briefing document: Denosumab 2010
9. Langdahl BL et al. A 24-Month Study Evaluating the Efficacy and Safety of Denosumab for the Treatment of Men With Low BMD: Results From the ADAMO Trial. *J Clin Endocrinol Metab* 2015;100(4):1335-42.
10. Orwoll E et al. A randomized, placebo-controlled study of the effects of denosumab for the treatment of men with low BMD. *J Clin Endocrinol Metab* 2012;97(9):3161-69.

Launch date: June 2010 Manufacturer: Amgen

WARNING: This sheet should be read in conjunction with the Summary of Product Characteristics
This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging

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