

denosumab, 60mg solution for injection in a pre-filled syringe (Prolia®)
SMC No. (651/10)

Amgen

05 November 2010

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

denosumab (Prolia®) is accepted for restricted use within NHS Scotland.

Indication under review: treatment of osteoporosis in postmenopausal women at increased risk of fractures. Denosumab significantly reduces the risk of vertebral, non vertebral and hip fractures.

SMC restriction: use only in patients with a bone mineral density (BMD) T-score < -2.5 and ≥ -4.0 for whom oral bisphosphonates are unsuitable due to contraindication, intolerance or inability to comply with the special administration instructions.

Treatment with denosumab for three years significantly reduced the incidence of new vertebral, non-vertebral and hip fractures compared with placebo in postmenopausal women at increased risk of fractures.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

Treatment of osteoporosis in postmenopausal women at increased risk of fractures. Denosumab significantly reduces the risk of vertebral, non vertebral and hip fractures.

Dosing Information

60mg by a single subcutaneous injection once every 6 months into the thigh, abdomen or back of arm.

Product availability date

3 June 2010

Summary of evidence on comparative efficacy

Denosumab is the first in a new class of drugs to treat osteoporosis. It is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to receptor activator of nuclear factor- κ B ligand (RANKL), preventing activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption in cortical and trabecular bone.

The submitting company has requested that the Scottish Medicines Consortium considers the use of this product in a sub-population of the licensed indication i.e. in patients for whom oral bisphosphonates are unsuitable due to contraindication, intolerance or inability to comply with their special administration instructions.

Evidence to support efficacy is from one double-blind, randomised, placebo-controlled study of the effect of denosumab on fracture prevention in postmenopausal women, 60 to 90 years with bone mineral density (BMD) T-score (total hip or lumbar spine) < -2.5 but ≥ -4.0 . Prior treatment with oral bisphosphonates was permitted if the treatment duration was ≤ 3 years and had ended at least one year before recruitment. The frequency and duration of prior bisphosphonate use was comparable between treatment groups. Patients were randomised equally to receive denosumab 60mg or placebo subcutaneously every 6 months for 36 months (last dose at 30 months) and were stratified according to 5-year age groups. All patients received daily calcium (≥ 1 g) and vitamin D (≥ 400 IU) supplementation.

A total of 7,868 patients were initially randomised but 60 patients (31 denosumab and 29 placebo) at one site were excluded from all analyses due to protocol violations, leaving 7,808 patients subsequently considered to be the whole study population.

The primary endpoint was the incidence at 3 years of new vertebral fractures comprising clinical fractures (that the patient would be aware of and seek medical attention) and morphometric fractures (that could only be diagnosed radiographically). The primary efficacy sub-set included all patients who underwent spinal radiography at baseline and had at least one subsequent visit. Last fracture status was carried forward for patients lost to follow up or who withdrew before a fracture event.

The incidence of new radiographic vertebral fractures at 3 years was 2.3% (86/3,702) and 7.2% (264/3,691) for patients receiving denosumab and placebo, respectively. This represents a relative reduction in risk of 68% for denosumab, risk ratio (RR) 0.32 (95% confidence interval [CI] 0.26 to 0.41).

Secondary endpoints were time to first non-vertebral fracture and time to first hip fracture and a tertiary endpoint was time to new clinical vertebral fracture. Calculations of these outcomes were based on Kaplan-Meier estimates of a 36 month cumulative incidence in the full treatment groups, 3,902 denosumab and 3,906 placebo patients. Denosumab was reported to have significantly reduced the risk of non-vertebral fracture: cumulative incidence 6.5% compared with 8.0% for placebo (hazard ratio (HR) 0.80 (95% CI 0.67 to 0.95), a 20% relative risk reduction.

Denosumab reduced the risk of hip fracture relative to placebo, cumulative incidence 0.7% versus 1.2% for denosumab and placebo, respectively, HR 0.60 (95% CI 0.37 to 0.97), a 40% relative risk reduction.

Denosumab reduced new clinical vertebral fractures relative to placebo, 0.8% versus 2.6% RR 0.31 (95% CI 0.20 to 0.47) (cumulative Kaplan-Meier estimate).

Denosumab produced a relative increase in bone mineral density of 9.2% (95% CI 8.2 to 10.1) in lumbar spine and 6.0% (95% CI 5.2 to 6.7) in total hip relative to placebo. Denosumab also reduced bone turnover markers serum C-telopeptide and serum procollagen type 1 N-terminal propeptide by 72% and 76%, respectively relative to placebo at 36 months.

Summary of evidence on comparative safety

The pivotal study found no significant differences between denosumab and placebo in the incidence of adverse events (AEs), serious AEs, or discontinuations due to AEs. There was also no difference between treatment groups in the incidence of death, cancer, cardiovascular events or infections. No patients developed neutralising antibodies to denosumab.

Eczema was reported in significantly more patients receiving denosumab than placebo, 3.0% and 1.7%, respectively. Cellulitis was reported as an SAE in significantly more denosumab patients than placebo patients (0.3% [n=12] versus <0.1% [n=1]).

Denosumab has a novel mechanism of action that could potentially affect the immune system. Information on long-term use is limited. The European Medicines Agency (EMA) has asked the company to carry out a study in women with postmenopausal osteoporosis to investigate the following risks: hypocalcaemia leading to hospitalisation, osteonecrosis of the jaw, infections leading to hospitalisation, hypersensitivity leading to hospitalisation, fracture healing complications and malignancies.

Summary of clinical effectiveness issues

The submitting company has requested that the Scottish Medicines Consortium considers the use of this product in a sub-population of the licensed indication i.e. in patients for whom oral bisphosphonates are unsuitable due to contraindication, intolerance or inability to comply with their special administration instructions.

The pivotal study, which reflects the licensed population, demonstrated that, compared with placebo, treatment with denosumab for 3 years significantly reduced new radiographic vertebral fractures in postmenopausal women with osteoporosis and also demonstrated a significant reduction of the incidence of hip fractures and non-vertebral fractures. The EMA considered that the study was adequately sized, designed and performed and the efficacy results were equal to or better than what has earlier been demonstrated for other drugs approved for the treatment of osteoporosis in postmenopausal women at increased risk of fracture.

The primary endpoint included morphometric fractures which can only be diagnosed radiographically and in practice would not normally be diagnosed and treated. It has been reported that most vertebral fractures remain undiagnosed. Denosumab significantly reduced new clinical vertebral fractures by 69% compared with placebo; however this was a tertiary endpoint.

A random effects indirect comparison (Bucher method) concluded that denosumab significantly lowered the risk of new vertebral fracture compared with strontium and raloxifene. However, there was substantial heterogeneity in patient and baseline disease characteristics, study duration and quality. Five of the ten studies investigated raloxifene, two strontium and one each denosumab, zoledronic acid and (oral, not intravenous) ibandronic acid. A mixed treatment comparison with meta-regression would have been preferable. Therefore the conclusions of the indirect comparison cannot be confirmed.

If used in accordance with the manufacturer's proposed positioning, denosumab would provide an alternative to the small range of current treatment options for patients unable to receive oral bisphosphonates but whose osteoporosis is not sufficiently severe to be eligible for alternative drugs. It would also be a valuable treatment option in patients with severe renal impairment as denosumab is the only treatment considered safe to use in these patients.

The subcutaneous formulation may allow administration in primary care, unlike iv zoledronic acid and iv ibandronic acid, and SMC experts have indicated that they expect denosumab would be initiated in hospital and continued in primary care if appropriate service provision arrangements were in place. Although theoretically the subcutaneous injection could be self-administered, the mean age of the patient population and the long interval between injections suggest this is unlikely. Denosumab has a potential compliance advantage over strontium ranelate and raloxifene which require daily dosing.

As study data indicate that bone formation returns to base levels within one year after the cessation of denosumab therapy continued treatment is required to maintain its effect.

Other data were also assessed but remain commercially confidential.*

Summary of comparative health economic evidence

The manufacturer submitted a lifetime cost utility analysis comparing denosumab to raloxifene, strontium, iv ibandronic acid and iv zoledronic acid as a treatment option when oral bisphosphonates are unsuitable. An additional analysis comparing denosumab to no treatment was also presented. A Markov cohort model was used comprising 8 health states relating to hip, vertebral, wrist and other osteoporotic fractures. The mean treatment duration was 5 years with patients assumed to experience an additional 1 year of benefit after treatment is stopped.

Clinical data used in the economic model came from a meta-analysis of placebo controlled studies using fracture efficacy endpoints. Fracture risk was estimated by combining the general population risk, the relative risk of fracture in patients with osteoporosis from the literature and the relative risk reductions from treatment from the indirect comparison. Mortality estimates post-fracture were also included. Resource use included in the model covered the treatment of fractures, DEXA scans and residential nursing home costs. It was assumed that denosumab treatment would be initiated in secondary care and continued in primary care, whereas iv injections were assumed to be provided in secondary care only. Utility values relating to the different fracture events were taken from literature sources and adjusted using age-related population norms. In the base case patients were aged 70 years with BMD T-score ≤ -2.5 and the results were presented separately according to previous fracture history.

In patients with no prior fracture the manufacturer estimated the following incremental cost effectiveness ratios (ICERs):

Denosumab vs:	Incremental cost	Incremental quality adjusted life year (QALY)	ICER
Strontium	-£19	0.0427	Denosumab dominates
Raloxifene	£352	0.0387	£9,110
iv Ibandronic acid	-£3,010	0.0367	Denosumab dominates
iv Zoledronic acid	-£979	-0.006	*£162,924
No treatment	£1,823	0.062	£29,407

*denosumab is estimated to be less costly but also less effective than iv zoledronic acid.

In patients with prior fracture the manufacturer estimated the following ICERs:

Denosumab vs:	Incremental cost	Incremental QALY	ICER
Strontium	-£149	0.0808	Denosumab dominates
Raloxifene	£127	0.0636	£2,005
iv Ibandronic acid	-£3,221	0.0688	Denosumab dominates
iv Zoledronic acid	-£988	-0.0148	*£66,670
No treatment	£1,668	0.1321	£12,631

*denosumab is estimated to be less costly but also less effective than iv zoledronic acid.

The manufacturer provided additional sensitivity analysis which removed the non-significant differences in the relative risks of fractures versus placebo from the model (based on the meta-analysis of placebo controlled studies). This slightly reduced the ICERs versus strontium and in the comparison with iv zoledronic acid resulted in a small increase in the QALY loss.

A further analysis, which only included the statistically significant differences in relative risks between the treatments (based on the indirect comparison), resulted in the ICERs increasing across all the comparisons but still remaining within acceptable limits (highest ICER was £17,269 versus raloxifene in patients with no prior fracture).

Some other issues were noted:

- There is uncertainty about how denosumab would be administered in practice as there may be some reluctance to administer denosumab in primary care and an enhanced service fee may apply. However, sensitivity analysis was provided by the manufacturer to show that the results were relatively insensitive to changes in the assumptions regarding where treatment would be administered.
- In the comparison with no treatment the ICER for patients with no prior fracture is relatively high (£29k) and is sensitive to the time horizon and baseline fracture risk.
- The utility values used in the model may be quite low, particularly in relation to the assumption that patients in the post hip fracture and post vertebral fracture health states continue to experience relatively poor quality of life for the subsequent duration of the model. However, the values used are broadly comparable to previous submissions for osteoporosis treatments and additional sensitivity analysis was provided to further test this aspect of the model.

Other data were also assessed but remain commercially confidential.*

Summary of patient and public involvement

A Patient Interest Group submission was received from the National Osteoporosis Society.

Additional information: guidelines and protocols

The National Institute of Health and Clinical Excellence (NICE) published the following two technology appraisals. Only guidance relevant to comparators is quoted below.

TA 160: Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women, (amended) October 2008, (amended January 2010). Strontium ranelate is recommended as an alternative treatment option for the primary prevention of osteoporotic fragility fractures in postmenopausal women who are unable to comply with the special instructions for the administration of alendronate and either risedronate or etidronate, or have a contraindication to or are intolerant of alendronate and either risedronate or etidronate and who also have a specified combination of T-score, age and number of independent clinical risk factors for fracture. Raloxifene is not recommended as a treatment option for the primary prevention of osteoporotic fragility fractures in postmenopausal women.

TA 161: Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women, October 2008 (amended, January 2010).

Strontium ranelate and raloxifene are recommended as alternative treatment options for the secondary prevention of osteoporotic fragility fractures in postmenopausal women who are unable to comply with the special instructions for the administration of alendronate and either risedronate or etidronate, or have a contraindication to, or are intolerant of, alendronate and either risedronate or etidronate and who also have a specified combination of T-score, age and number of independent clinical risk factors for fracture. Teriparatide is recommended as an alternative treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women who are unable to take alendronate and either risedronate or etidronate, or have a contraindication to or are intolerant of alendronate and either risedronate or etidronate, or who have a contraindication to, or are intolerant of strontium ranelate or who have had an unsatisfactory response to treatment with alendronate, risedronate or etidronate and who are 65 years or older and have a T-score of -4.0 SD or below, or a T-score of -3.5 SD or below plus more than two fractures, or who are aged 55–64 years and have a T-score of -4 SD or below plus more than two fractures.

The Scottish Intercollegiate Guidelines Network guidance, Management of Osteoporosis was published in 2003 and is currently being updated. The expected completion date is spring 2013.

The National Osteoporosis Guideline group published a Guideline for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK in 2008. It states that in individuals who are intolerant of alendronate or in whom it is contraindicated, other bisphosphonates, strontium ranelate or raloxifene may provide appropriate treatment options. The high cost of parathyroid hormone peptides restricts their use to those at very high risk, particularly for vertebral fractures.

Additional information: comparators

Zoledronic acid iv infusion, ibandronic acid iv injection, strontium ranelate (oral), raloxifene (oral), teriparatide, and parathyroid hormone (recombinant).

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Denosumab	60mg subcutaneously every 6 months	366
Recombinant human parathyroid hormone	100 micrograms subcutaneously daily	4,062
Teriparatide	20 micrograms subcutaneously daily	3,534
Strontium ranelate	2g orally daily	333
Ibandronic acid	3mg intravenously every 3 months	275
Zoledronic acid	5mg intravenously once a year	267
Raloxifene	60mg orally daily	258

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 25 August 2010.

Additional information: budget impact

The manufacturer estimated between 956 and 1,541 patients would be treated in year 1 rising to between 3,283 and 5,548 in year 5. The budget impact estimates assume denosumab would receive 10% market share of drugs other than oral bisphosphonates and 50% share of patients currently receiving no treatment in year 1, rising to 50% and 90% respectively in year 5. Based on the lower estimate of patient numbers the manufacturer estimated the drug budget impact would be £223k in year 1 rising to £528k in year 5. Using the higher estimate of patient numbers the manufacturer estimated the drug budget impact would be £419k in year 1 rising to £1.1m in year 5. SMC experts suggested that these figures may underestimate net budget impact.

References

The undernoted references were supplied with the submission. The reference shaded grey is additional to that supplied with the submission.

Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al.; FREEDOM Trial. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009 Aug 20; 361(8):756-65.

The European Medicines Agency (EMA) CHMP Assessment Report Denosumab (Prolia®). 18/03/2010, EMEA/H/C/001120 www.emea.europa.eu

This assessment is based on data submitted by the applicant company up to and including **15 October 2010**.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:

http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Release_of_Company_Data

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.