AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Denosumab (Prolia®) for the treatment of osteoporosis in men at increased risk of fractures

July 2018

ONE WALES INTERIM COMMISSIONING DECISION

Denosumab (Prolia®) for the treatment of osteoporosis in men at increased risk of fractures

Date of original advice: March 2017
Date of review: March 2018

The following Interim Pathways Commissioning Group (IPCG) recommendation has been endorsed by health board Chief Executives.

Denosumab (Prolia®) can continue to be made available within NHS Wales for the treatment of osteoporosis in men at increased risk of fractures. Denosumab (Prolia®) should only be made available for men who fulfil the agreed criteria for treatment.

This advice will be reviewed in 12 months or earlier if new evidence becomes available.

Advice is interim to subsequent Health Technology Appraisal advice from AWMSG or NICE becoming available.

Clinician responsibility
Clinicians will be obliged to collect and monitor patient outcomes. Evidence of clinical outcomes will be taken into consideration when reviewing the One Wales Interim Commissioning decision.

Health board responsibility
Health boards will take responsibility for implementing One Wales Interim Commissioning decisions and ensuring that a process is in place for monitoring clinical outcomes.

One Wales advice promotes consistency of access across NHS Wales.

Criteria for treatment with denosumab (Prolia®) for the treatment of osteoporosis in men at increased risk of fractures

These criteria have been adapted from NICE Technology Appraisal guideline TA204 Denosumab for the prevention of osteoporotic fractures in postmenopausal women[1].

Denosumab (Prolia®) can be made available for the primary prevention of osteoporotic fractures in men at increased risk of fractures:

- Who are unable to comply with the special instructions for administering alendronate and risedronate, or have an intolerance of, or a contraindication to, those treatments,
- Who are unsuitable for treatment with intravenous (IV) zoledronic acid and
- Who have a combination of bone mineral density T-score, age and number of independent risk factors as shown in the table below:

T-scores at or below which denosumab is recommended when oral bisphosphonates are not suitable

	Number of independent clinical risk factors*		
Age (years)	**0**	**1**	**2**
65–69	Not recommended	-4.5	-4.0
70–74	-4.5	-4.0	-3.5
≥ 75	-4.0	-4.0	-3.0
*Independent clinical risk factors are: parental history of hip fracture; alcohol intake of 4 or more units per day; and rheumatoid arthritis.			

Denosumab (Prolia®) can be made available for the secondary prevention of osteoporotic fragility fractures in men at increased risk of fractures who are unable to comply with the special instructions for administering alendronate and risedronate, or have an intolerance of, or a contraindication to, those treatments and who are unsuitable for treatment with IV zoledronic acid.

1. National Institute for Health and Care Excellence. Technology Appraisal 204. Denosumab for the prevention of osteoporotic fractures in postmenopausal women. Oct 2010.

Background
Denosumab was first licensed in May 2010 for the treatment of osteoporosis in postmenopausal women and for the treatment of bone loss associated with hormone ablation in men with prostate cancer[1]. In June 2014 the European Medicines Agency granted an extension to the licence of denosumab to include the treatment of osteoporosis in men at increased risk of fractures[2]. The National Institute for Health and Care Excellence (NICE) are currently in the process of appraising denosumab for this indication as part of a multiple technology appraisal[3]. Clinicians in Wales consider there is an unmet need for this medicine in men and have identified a cohort of patients who could benefit from this treatment.

Current One Wales Interim Commissioning Decision
Denosumab (Prolia®) can be made available within NHS Wales for the treatment of osteoporosis in men at increased risk of fractures. Denosumab (Prolia®) should only be made available for men who fulfil the agreed criteria for treatment. March 2017.

Licence status
Denosumab was licensed in June 2014 for the treatment of osteoporosis in men at increased risk of fractures[2].

Guidelines
Updated National Osteoporosis Group guideline published March 2017 (NOGG 2017): clinical guideline for the prevention and treatment of osteoporosis[4]. NOGG 2017 recommends the oral bisphosphonates, alendronate and risedronate, as first line treatments for osteoporosis in men. Where these are contraindicated or not tolerated, NOGG 2017 advises that zoledronic acid or denosumab provide the most appropriate alternatives, with teriparatide as an additional option. In men with or without a fragility fracture the management strategy should be based on the ten-year probability of a major osteoporotic fracture[4].

Health Technology Appraisal advice for alternative medicines
NICE TA464: oral and intravenous bisphosphonates are recommended as options for treating osteoporosis in adults[5]. This technology appraisal established at what level of absolute fracture risk bisphosphonates are cost-effective and should be applied in conjunction with the NICE guideline on assessing the risk of fragility fractures (CG146)[6], which defines who is eligible for osteoporotic fracture risk assessment, and the NICE quality standard on osteoporosis (QS149)[7], which defines the clinical intervention thresholds for the 10 year fracture probability of a major osteoporotic fracture. Oral bisphosphonates and zoledronic acid are recommended where the 10 year probability of osteoporotic fracture is at least 1% and 10%, respectively. Where oral bisphosphonates are difficult to take, contraindicated or not tolerated then zoledronic acid may be used where the 10 year probability is at least 1%[5].

Efficacy/Effectiveness
A repeat literature search identified an extension study to the FREEDOM study which was described in the original evidence status report[8]. FREEDOM was a phase III randomised control study in postmenopausal women. This study was included in the licence application for men as studies in men did not investigate the anti-fracture efficacy of denosumab, and a similar association between bone mineral density and fracture risk has been reported in men and in postmenopausal women. All participants who completed the FREEDOM trial without discontinuing treatment or missing more than one dose of investigational product were eligible to enrol in the open-label, seven-year extension study, in which all participants received denosumab. The data represent up to ten years of denosumab treatment for women who received three years of denosumab in FREEDOM and continued in the extension (long-term group), and up to seven years for women who received three years of placebo and transitioned to denosumab in the extension (cross-over group). The primary outcome was safety monitoring (see safety section). Secondary endpoints included new vertebral, hip, and non-vertebral fractures as well as bone mineral density at the lumbar spine, total hip, femoral neck, and one-third radius[8].

Of the 4,550 women who enrolled in the study, 2,626 completed the study[8]. The yearly incidence of new vertebral fractures (ranging from 0.90% to 1.86%) and non-vertebral fractures (ranging from 0.84% to 2.55%) remained low during the extension, similar to rates observed in the denosumab group during the first three years of the FREEDOM study. In the long-term group, bone mineral density increased from FREEDOM baseline by 21.7% at the lumbar spine, 9.2% at total hip, 9.0% at

femoral neck, and 2.7% at the one-third radius. In the cross-over group, bone mineral density increased from extension baseline by 16.5% at the lumbar spine, 7.4% at total hip, 7.1% at femoral neck, and 2.3% at one-third radius[8].

The repeat literature search also identified a study, presented as a conference abstract, which assessed the risk of subsequent fractures among patients experiencing a fracture on FREEDOM and the extension studies[9]. In the FREEDOM study, 438 women who received placebo and 272 women who received denosumab had an osteoporotic fracture. Of these, 54 (12.3%) women in the placebo group and 24 (8.8%) women in the denosumab group had at least one subsequent fracture. The adjusted subject incidence per 100 patient-years was lower for denosumab (6.7) compared with placebo (10.1). Combining all of the women who received denosumab from the FREEDOM and the extension studies, 794 (13.7%) had an osteoporotic fracture and 144 (18.1%) of these women experienced at least one subsequent fracture. The adjusted subject incidence was 5.8 per 100 patient-years. Of the women who had at least one subsequent fracture, 90% only experienced one fracture, and spine fracture was most frequent. The abstract concluded that the risk of having a subsequent on-study osteoporotic fracture was lower in women who received denosumab treatment compared with placebo (hazard ratio 0.60; 95% confidence interval [CI] 0.43 to 0.81; p = 0.0012). This suggests that a fracture sustained while on denosumab is not necessarily indicative of treatment failure, and treatment continuation should be considered[9].

A systematic review and meta-analysis, which included 22 randomised control studies of osteoporosis treatment for men that reported fracture outcomes, has been published since the original evidence status report[10]. Of the 22 studies evaluated only 2 included a denosumab treatment arm. Sufficiently similar studies were available for separate meta-analyses for the outcome of vertebral fractures for alendronate, calcitonin, denosumab and risedronate. A significantly lower risk of vertebral fractures was demonstrated with alendronate (relative risk [RR] = 0.328, 95% CI = 0.155–0.692) and risedronate (RR = 0.428, 95% CI = 0.245 to 0.746), but not with calcitonin (RR = 0.272, 95% CI = 0.046 to 1.608) or denosumab (RR = 0.256, 95% CI = 0.029 to 2.238) than in controls. The meta analyses were limited by the small number of similar studies assessing each medicine and small sample sizes in many of the studies. The authors concluded that further studies are needed to evaluate the efficacy of nonbisphosphonates in men[10].

Safety

The primary outcome of the extension to the FREEDOM study, described above, was safety monitoring[8]. The yearly exposure-adjusted participant incidence of adverse events for all individuals receiving denosumab decreased from 165.3 to 95.9 per 100 participant-years over the course of ten years. Serious adverse event rates were generally stable over time, varying between 11.5 and 14.4 per 100 participant-years. One atypical femoral fracture occurred in each group during the extension. Seven cases of osteonecrosis of the jaw were reported in the long-term group and six cases in the crossover group[8].

The repeat literature search also identified a cohort study comparing the safety of denosumab versus zoledronic acid, within one year of starting treatment, in patients with osteoporosis (96% were female) from the United States, aged 50 years or above[11]. The study showed that denosumab was not associated with an increased risk of serious infection or cardiovascular disease, compared with zoledronic acid[11].

The termination of denosumab treatment has been shown to be associated with rapid bone loss[4]. It is unclear whether this results in an increase in fracture risk, but there are case reports of vertebral fractures, often multiple, occurring within 18 months after stopping treatment. Although further studies are required in patients who stop denosumab treatment, NOGG 2017 advises that switching to an alternative therapy, such as a bisphosphonate, should be considered[4].

In June 2017, the Medicines and Healthcare products Regulatory Agency published a Drug Safety Update article about reports of osteonecrosis of the external auditory canal with denosumab[12]. This followed a 2015 Drug Safety Update about very rare reports of osteonecrosis of the external auditory canal with bisphosphonates. Worldwide, five reports of osteonecrosis of the external auditory canal

have been received for patients treated with 60 mg denosumab for osteoporosis[12]. A warning has now been included in the Summary of Product Characteristics for denosumab (Prolia®)[13].

Cost effectiveness
There is no new significant cost-effectiveness evidence since that provided in the original evidence status report.

Budget impact
Since 2017, 101 men in Wales have received denosumab treatment in line with the One Wales decision. This is in agreement with the estimated patient numbers provided by clinical experts to inform the original One Wales decision; clinical experts estimated 80–100 male patients in the third line setting and 20–30 male patients in the fourth line setting.

Welsh commercial access agreement
At the time of the original evidence report, the company did not consider a commercial agreement as they believed this is supported by the likely limited budget impact and the results of the Swedish cost-effectiveness study, which indicates that denosumab is cost dominant compared to a range of comparators. Additionally, as denosumab has been approved by NICE for the prevention of osteoporotic fractures in postmenopausal women at its UK list price and has demonstrated similar tolerability and increases in bone mineral density in men to that observed in postmenopausal women, the company believed that denosumab would represent a similar cost-effective treatment option in the male population and have a manageable budget impact.

Impact on health and social care services
This remains minimal.

Patient outcome data
It is difficult to report meaningful outcome data after 12 months of availability due to the chronic nature of osteoporosis and the twice yearly dose of denosumab.

References

1. European Medicines Agency. Authorisation details: Prolia®. June 2017. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001120/human_med_001324.jsp&mid=WC0b01ac058001d124. Accessed Feb 2018.
2. European Medicines Agency. Prolia®. Procedural steps taken and scientific information after the authorisation. Jan 2018. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/001120/WC500107471.pdf. Accessed Feb 2018.
3. National Institute for Health and Care Excellence. Technology Appraisal in development GID-TA10072. Non-bisphosphonates for treating osteoporosis. Expected publication date: TBC. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10072. Accessed Feb 2018.
4. National Osteoporosis Guideline Group. NOGG 2017: Clinical guideline for the prevention and treatment of osteoporosis. March 2017. Available at: https://www.sheffield.ac.uk/NOGG/NOGG%20Guideline%202017.pdf. Accessed Feb 2018.
5. National Institute for Health and Care Excellence. Technology Appraisal 464. Bisphosphonates for treating osteoporosis. Published date: Aug 2017. Last updated: Feb 2018. Available at: https://www.nice.org.uk/guidance/ta464. Accessed Feb 2018.
6. National Institute for Health and Care Excellence. Clinical Guideline, CG146. Osteoporosis: assessing the risk of fragility fracture. Published date: Aug 2012. Last updated: Feb 2017. Available at: https://www.nice.org.uk/guidance/cg146. Accessed Feb 2018.
7. National Institute for Health and Care Excellence. Quality Standard, QS149. Osteoporosis. April 2017. Available at: https://www.nice.org.uk/guidance/qs149. Accessed Feb 2018.
8. Bone H, Wagman R, Brandi M et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. *The Lancet. Diabetes & Endocrinology.* 2017;5(7):513-523.
9. Kendler D, Chines A, Brandi M et al. The risk of subsequent osteoporotic fractures is decreased in patients experiencing fracture while on denosumab: results from the FREEDOM and FREEDOM extension studies [Abstract]. 11-16 November 2016. *Arthritis and Rheumatology*. 68 (suppl 10). http://acrabstracts.org/abstract/the-risk-of-subsequent-osteoporotic-fractures-is-decreased-in-patients-experiencing-fracture-while-on-denosumab/. Accessed Feb 2018.

10. Nayak S, and Greenspan S. Osteoporosis treatment efficacy for men: a systematic review and meta-analysis. *Journal of the American Geriatrics Society.* 2017;65(3):490-495.
11. Choi N, Solomon D, Tsacogianis T et al. Comparative safety and effectiveness of denosumab versus zoledronic acid in patients with osteoporosis: a cohort study. *Journal of Bone and Mineral Research.* 2017;32(3):611-617.
12. Medicines and Healthcare products Regulatory Agency. Drug safety update. Denosumab (Prolia, Xgeva▼): reports of osteonecrosis of the external auditory canal. June 2017. Available at: https://www.gov.uk/drug-safety-update/denosumab-prolia-xgeva-reports-of-osteonecrosis-of-the-external-auditory-canal. Accessed Feb 2018.
13. Amgen Ltd. Prolia®. Summary of Product Characteristics. Sept 2017. Available at: https://www.medicines.org.uk/emc/product/568. Accessed Feb 2018.