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

August 2019

ONE WALES INTERIM COMMISSIONING DECISION

Denosumab for the treatment of osteoporosis in men at increased risk of fractures

Date of original advice: March 2017
Date of review: August 2019

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

Denosumab can continue to be made available within NHS Wales for the treatment of osteoporosis in men at increased risk of fractures. Denosumab 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 assessment advice from the All Wales Medicines Strategy Group (AWMSG) or the National Institute for Health and Care Excellence (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 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 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 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.

One Wales Interim Commissioning Process
Interim Pathways Commissioning Group (IPCG) summary of decision rationale

Medicine: **denosumab**
Indication: **treatment of osteoporosis in men at increased risk of fractures**
Meeting date: **29 April 2019**

Criteria	IPCG opinion
Clinical effectiveness	IPCG accepts that the new clinical evidence supports the current One Wales decision. No new relevant medicines or health technology assessment advice has been identified that would alter treatment choice. A NICE multiple technology appraisal which includes denosumab is expected September 2019. The current place in therapy remains the same. No new safety issues have been reported.
Cost-effectiveness	IPCG considers that the new cost effectiveness evidence supports the current One Wales decision.
Budget impact	IPCG notes that the number of patients who received denosumab for this indication in 2018 is less than estimates used to inform the original One Wales decision.
Final recommendation	IPCG recommends that the current One Wales decision should remain unchanged.
Summary of rationale	IPCG are content that there is no new significant information or evidence to warrant a full reassessment of denosumab.

This is a summary of new evidence available and patient outcome data collected, to inform the review.

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 (EMA) 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) is currently in the process of appraising denosumab for the treatment of osteoporosis as part of a multiple technology appraisal (expected publication date September 2019)[3]. One Wales advice is interim to health technology assessment advice. 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 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. March 2018.

Licence status
Denosumab was licensed in June 2014 for the treatment of osteoporosis in men at increased risk of fractures[2]. In June 2018, the licence was extended to include the treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture[2].

Guidelines
In June 2018, NHS England concluded to commission teriparatide as an alternative treatment option for the secondary prevention of osteoporotic fragility fractures in men[4]. This recommendation is interim to NICE guidance[4]. Teriparatide is not recommended for use within NHS Wales for the treatment of osteoporosis in men at increased risk of fracture[5].

Health Technology Assessment advice for alternative medicines
There are no relevant new medicines or health technology assessment advice.

Efficacy/Effectiveness
NICE's assessment report for the multiple technology appraisal in progress has been published[6]. The NICE assessment report is still under consultation and may be subject to change based on feedback from consultees and commentators. The assessment investigated the clinical effectiveness and cost effectiveness of denosumab, raloxifene, romosozumab and teriparatide, within their licensed indications (includes men and women), for the prevention of osteoporotic fragility fractures compared against each other, bisphosphonates or placebo[6]. Romosozumab does not currently have a marketing authorisation in the UK for treating osteoporosis and the results for this medicine have therefore been excluded from this review. A systematic review of the literature and network meta-analyses were conducted[6]. Pairwise analyses for denosumab versus placebo or zoledronic acid and for teriparatide versus denosumab were conducted; results are shown in Table 1[6]. Denosumab was associated with beneficial treatments effects versus placebo for all measures with the exception of wrist fractures; the benefit was statistically significant for vertebral and hip fractures and for femoral neck bone mineral density. Treatment effects for denosumab on wrist fractures were based on one small study and therefore treatment effects are highly uncertain. No significant difference in effects were demonstrated for denosumab versus zoledronic acid, although results favoured denosumab for vertebral and hip fractures. Teriparatide was associated with statistically significant beneficial treatment effects for non-vertebral fractures compared with denosumab. For all fracture measures teriparatide was favoured over denosumab although the results were not statistically significant[6].

Table 1. Hazard ratios of pairwise comparisons for each of the five main fracture types and for femoral neck bone mineral density

	Denosumab vs placebo HR (95% CrI)	Denosumab vs zoledronic acid HR (95% CrI)	Teriparatide vs denosumab HR (95% CrI)
Vertebral fractures	**0.30 (0.21 to 0.43)**	0.77 (0.46 to 1.19)	0.76 (0.46 to 1.20)
Non-vertebral fractures	0.86 (0.69 to 1.12)	1.18 (0.91 to 1.63)	**0.68 (0.47 to 0.94)**
Hip fractures	**0.56 (0.31 to 0.94)**	0.88 (0.46 to 1.59)	0.62 (0.24 to 1.58)
Wrist fractures	1.29 (0.15 to 12.49)	NR	0.57 (0.05 to 5.17)
Humerus fractures	0.55 (0.12 to 2.41)	NR	1.00 (0.20 to 5.02)
Femoral neck BMD*	**3.36 (2.74 to 3.97)**	0.19 (−0.70 to 1.09)	−0.78 (−1.57 to 0.01)

*Absolute difference in HR of pairwise comparisons compared with placebo
BMD: bone mineral density; CrI: credible interval; HR: median hazard ratio; NA: not available; NR: not reported; vs: versus
NB: figures in bold are statistically significant

The repeat literature search identified the publication of a post-hoc analysis of the FREEDOM and FREEDOM extension studies that was included in the last One Wales review as a conference abstract[7,8]. The results are as previously reported[7].

Safety

No new safety issues were identified. In the assessment report published by NICE, the ranges of serious adverse event rates were comparable for all non-bisphosphonates: denosumab 2% to 25.8%; raloxifene 2% to 18.6%; teriparatide 0% to 33.0%[6]. Across studies reporting mortality, there were no significant differences between non-bisphosphonate treatment arms and their comparators of placebo, other non-bisphosphonates or bisphosphonates[6].

Cost effectiveness

In the assessment report published by NICE, at a FRAX risk of 25.1%, denosumab compared with zoledronic acid is associated with an incremental quality-adjusted life-year (QALY) gain of 0.0045 and a QALY loss of 0.0002 when compared with teriparatide[6]. When considered together with incremental costs, denosumab is unlikely to be cost-effective compared to zoledronic acid using conventional thresholds. However, denosumab is likely to be a worthwhile treatment option when compared to teriparatide, as it is associated with a small QALY loss but a notable cost saving of £3,882. Comparative analyses produced similar conclusions when varying FRAX risk from 3.1% to 25.1%[6]. The marketing authorisation holder is of the opinion that the cost-effectiveness model in the NICE assessment report may not be representative of the patient population or current NHS practice and may be subject to change following the consultation period.

Budget impact

Since 2018, 49 men in Wales have received denosumab for the first time treatment in line with the One Wales decision; an additional 134 patients continued treatment with denosumab from 2017. Therefore, the total number of patients who received denosumab in 2018 was 183. This is lower than the estimated patient numbers by clinical experts used to inform the original One Wales decision. Clinical experts estimated 80 to 100 male patients in the third line setting and 20 to 30 male patients in the fourth line setting eligible for treatment with denosumab per year. It was estimated that 86% of patients would continue treatment for two or more years which would equate to a total of 242 patients in Year 2 for both lines of therapy.

Impact on health and social care services
This remains minimal.

Patient outcome data
Although information on patient outcomes has been requested, these data remain outstanding.

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 2019.
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 2019.
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 Mar 2019.
4. NHS England. Interim clinical commissioning policy statement: teriparatide for osteoporosis in men (adults). 2018. Available at: https://www.england.nhs.uk/publication/interim-clinical-commissioning-policy-statement-teriparatide-for-osteoporosis-in-men-adults/. Accessed Jan 2019.
5. All Wales Medicines Strategy Group. Final Appraisal Recommendation - 2108. Teriparatide (Forsteo®) 20 micrograms/80 microlitres solution for injection. Oct 2008. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/306. Accessed Jan 2019.
6. National Institute for Health and Care Excellence. Non-bisphosphonates for treating osteoporosis [ID901]: assessment report. Jan 2019. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10072. Accessed Feb 2019.
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