Endocrinology Subcommittee of the Pharmacology and Therapeutics Advisory Committee (PTAC)

Meeting held on 17 May 2018

(minutes for web publishing)

Endocrinology Subcommittee minutes are published in accordance with the *Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016.*

Note that this document is not necessarily a complete record of the Endocrinology Subcommittee meeting; the relevant portions of the minutes relating to Endocrinology Subcommittee discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

The Endocrinology Subcommittee may:

(a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;

(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

(c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

These Subcommittee minutes will be reviewed by PTAC at its meeting on 9 & 10 August 2018, the record of which will be available in due course.

Record of the Endocrinology Subcommittee of PTAC teleconference held at PHARMAC on 17 May 2018

1 Denosumab for treatment of osteoporosis in men

Application

1.1 The Subcommittee considered a paper from PHARMAC staff on denosumab for the treatment of osteoporosis in men.

Recommendation

1.2 The Subcommittee **recommended** that denosumab be funded for men with osteoporosis by removal of the gender restrictions from the denosumab Special Authority with a high priority.

Discussion

1.3 The Subcommittee noted that PHARMAC had recently consulted on a proposal to fund denosumab for the treatment of severe, established osteoporosis in postmenopausal women who met certain clinical criteria including having received inadequate benefit from oral treatments and for whom zoledronic acid is contraindicated due to renal impairment.

1.4 The Subcommittee noted that, following consultation feedback, PHARMAC was seeking advice on the evidence for the use of denosumab in men with osteoporosis and how this compares to the evidence for its use in women with osteoporosis.

1.5 The Subcommittee noted that the criteria consulted on were those recommended by PTAC and were based on evidence reviewed by PTAC and the Endocrinology Subcommittee, which had only been in women. The Subcommittee noted that at the time of consultation, the Medsafe indication for denosumab was only for use in women.

1.6 The Subcommittee noted that the registered indication for denosumab had now been extended to include 'treatment to increase bone mass in men with osteoporosis at increased risk of fracture'.

1.7 The Subcommittee considered that there was good quality published evidence to show that while men with osteoporosis fracture less than women with osteoporosis, men who have a fracture have a higher mortality risk compared to women who have a fracture, and that men who fracture also have a lower quality of life (Haentjes et al Ann Intern Med 2010 Mar 16;152(6):380-90).

1.8 The Subcommittee considered that the most reliable data on osteoporosis rates by gender came from a study prepared for Osteoporosis New Zealand (Brown et al 2007) which showed that one man has an osteoporotic fracture for every three women. The Subcommittee considered that even though this study was ten years old, the rate remains applicable. Members considered that in New Zealand the prevalence of osteoporosis is increasing as has been observed in international

studies, which was in part due to increasing age of the population. Members also considered that treatment rates for osteoporosis in New Zealand were decreasing.

1.9 The Subcommittee noted the key clinical evidence of the use of denosumab in men comes from the ADAMO trial, a randomised controlled trial of men with osteoporosis who received either denosumab (60 mg day one and month six) or placebo for one year (Orwoll et al J Clin Endocrinol Metab 2012 Sep;97(9):3161-9), and from the ADAMO extension, an open-label, single arm trial extending denosumab treatment by another 12 months (Langdahl et al J Clin Endocrol Metab 2015 Apr;100(4):1335-42).

1.10 The Subcommittee noted that the mean age of patients in ADAMO was 65; patients as young as 30 could be included though only 6% of patients were aged under 50 years. Members considered that the study participants had a wide range of T-scores, and noted there were differences in ethnicity distributions between the two treatment arms. The Subcommittee considered that patients in ADAMO trial were less severe than in the key study of denosumab in women, the FREEDOM trial (Cummings et al N Engl J Med 2009 Aug 20;361(8):756-65). Members considered that this was not an indication of an intrinsic difference in severity between genders, since both men and women can have early onset, severe osteoporosis.

1.11 Members noted percentage change in lumbar spine bone mineral density from baseline at 12 months, the primary outcome, was reported to be 5.7% in the denosumab arm compared to 0.9% in the placebo arm (difference 4.8%, 95% CI 4.0-5.6%).

1.12 The Subcommittee considered that the ADAMO trial was high quality evidence that showed improvement in bone mineral density with denosumab use in men with osteoporosis. The Subcommittee considered that the ADAMO trial appeared to be the only currently available direct evidence for the use of denosumab in this patient group.

1.13 The Subcommittee considered there was good evidence for a correlation between bone mineral density and fracture rates both from studies of bisphosphonates generally and studies of denosumab in women, including the FREEDOM trial. The Subcommittee considered that bone mineral density is a very good surrogate marker for the benefit of denosumab.

1.14 The Subcommittee considered that there was no evidence to suggest that denosumab would have a different effect in men compared to women and no biological reason to expect that there might be. The Subcommittee considered that studies of other osteoporosis medications had not shown any difference in efficacy by gender.

1.15 The Subcommittee considered that the quality of evidence for denosumab was better in women than in men, as those trials were larger had longer follow-up, and were powered to examine changes in fracture incidence. Members considered that there may be a bias towards conducting osteoporosis research in women due to its higher prevalence.

1.16 Overall, the Subcommittee considered that the evidence showed that denosumab's benefits in reducing fracture risk are independent of gender.

1.17 The Subcommittee considered that it was appropriate to amend the proposed criteria for denosumab to remove restrictions on gender, and that gender restrictions should be removed rather than including men to ensure that non-binary patients are not excluded. Members considered that it may be appropriate to define eligible patients by age, such as restricting to patients who were either postmenopausal or at least 50 years old, although it was noted that the ADAMO trial did include a small number of patients under 50 years.

1.18 Members considered that there is published evidence available on the benefits of denosumab for premenopausal women, such as studies involving patients with cancer. Members discussed amending the criteria to include younger women. However, it was noted that this evidence had not yet been considered by the Subcommittee or by PTAC and also the current Medsafe registration for denosumab was limited to postmenopausal women.

1.19 The Subcommittee considered whether to replace 'postmenopausal' in the consulted criteria with the more technical definition used in the criteria for zoledronic acid for early breast cancer. The Subcommittee considered that 'postmenopausal' was simpler and clearer in the circumstances.

1.20 The Subcommittee considered that there were several aspects of the proposed criteria for denosumab not related to gender which should be reconsidered as they were potentially clinically inappropriate. Members considered that in particular the requirement to trial another agent was excessively restrictive given the patient group must be contraindicated to zoledronic acid due to renal impairment. Members considered that, in patients who had significant renal impairment, oral bisphosphonates would not be recommended. Members also considered that raloxifene has an increased stroke risk in women over 65 years and does not reduce the risk of non-vertebral fractures, making it a poor treatment choice in this group of patients. Members also noted that the proposed criteria do not include patients who have previously trialled intravenous zoledronic acid and had a reaction to it, or premenopausal women with a genetic disposition to osteoporosis.

1.21 The Subcommittee noted that the supplier of denosumab had provided an updated submission for the widening of access to denosumab, which included its use in many of these populations. The Subcommittee noted that consultation feedback had also been received regarding funding of denosumab for a number of different patient populations and that advice would be sought regarding the potential to widen access to denosumab in the future.