Senator Clare Moore,
Chair,
Senate Community Affairs Legislative Committee,
Inquiry into National Health (Pharmaceutical Benefits Scheme) Bill 2010

June 28, 2010

Dear Senator Moore,

We are writing in our capacity as the Medical Director and Chief Executive Officer of Osteoporosis Australia, respectively, and also represent the members of the Medical and Scientific Advisory Committee of Osteoporosis Australia to comment on the proposal by the PBAC to create a new Therapeutics Group that treats all oral bisphosphonates (the most common drugs used to prevent and treat osteoporosis) as equivalent to generic alendronate and therefore interchangeable at an individual patient level.

We understand that such interchangeability would mean in practice that when a patient with osteoporosis is being considered for treatment, the attending doctor would assume there is no difference whether he/she prescribes generic alendronate once-a-week or branded Fosamax or Actonel (which may be administered either weekly or monthly). The proposal also assumes the choice of either drug will make no practical difference to the patient or to their subsequent health outcomes.

However in reality, several substantial differences exist between alendronate and risedronate from a scientific perspective, as well as emerging evidence of differences between generic alendronate, and Fosamax and Actonel. These differences can impact on patients' compliance and persistence with therapy and effectiveness on fracture reduction, as shown below:

1. Bisphosphonate drugs are not all the same.

Differences in bisphosphonate drug function exist so there is a range of potency in the inhibition of enzymes affecting the survival of the cells that break down bone (osteoclasts) and in the binding of bisposphonates to bone mineral crystals. These are likely to be reflected in differences in time of onset of anti-fracture effectiveness and in the time for effects to wear off after treatment is stopped (1-5). In this regard, risedronate is one of the fastest to achieve an onset and offset of effects on bone.

2. Adverse events and poorer compliance.

The use of generic alendronate may be associated with increased gastrointestinal side effects compared with non-generic bisphosphonates (12-16) due to its differing dissolution in the gastrointestinal tract. This increase in indigestion is likely to lead to poorer compliance with more fractures being likely as a result (12, 13).

3. Generic alendronate does not come with calcium or vitamin D supplements.

Fosamax already comes combined with Vitamin D plus calcium supplements, Actonel comes with both Vitamin D plus calcium supplements. Generic alendronate does not come with either vitamin D or calcium. All the pivotal fracture studies with bisphosphonates were done using concomitant vitamin D and calcium supplementation, which means for most patients to achieve optimal benefits from bisphosphonates, vitamin D and calcium should also be given. However, pensioners in particular, and others often cannot afford the additional expense of vitamin D and calcium, which raises issues of equity of access. The non-generic bisphosphonates currently available in Australia allow for differential supplementation with either vitamin D or calcium in combination with the bisphosphonate. This flexibility would be lost by the proposal with potential harm to our patients using generic alendronate alone.

4. Constraints on administration regimens

Better compliance and persistence with bisphosphonates is associated with reduced fractures. Better compliance and persistence is also seen with less frequent drug dosing (22, 23), e.g. weekly vs. daily; once monthly; or annual administration. There is no once monthly formulation of generic alendronate, while risedronate may be given once a month, which is very likely to result in improved compliance.

5. Prevention of Steroid Osteoporosis

Only oral risedronate and intravenous zoledronic acid are approved for prevention of corticosteroid-induced osteoporosis in Australia, while Fosamax or generic alendronate are not. It would be incorrect for a non-approved drug to be supplied by pharmacists for this indication.

In conclusion, Osteoporosis Australia believes this new proposal, although cost-effective, is not consistent with the scientific evidence regarding bisphosphonate action. A more restrictive choice is likely to lead to poorer compliance and persistence with consequent adverse fracture outcomes. These adverse outcomes will cost Australia $388 million and result in 19,417 preventable fractures between now and 2020, based on a recent Access Economics report examining the cost of osteoporosis and preventable fractures to Australia (24). We therefore strongly oppose the proposal's uptake in Australia.

Yours sincerely,

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References:

Differences in Mechanism of action

1. Bisphosphonates: An Update on Mechanisms of Action and How These Relate to Clinical Efficacy, Russell G et al. Ann. N.Y. Acad. Sci. 2007 doi: 10.1196/annals.1402.089

2. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy, Russell G et al., Osteoporos Int 2008 DOI 10.1007/s00198-007-0540-8

3. Bisphosphonate efficacy and clinical trials for postmenopausal osteoporosis: Similarities and differences, Boonen S et al Bone 40 (2007) S26–S31

4. Randomized trial of effect of Alendronate continuation versus discontinuation in women With Low BMD: Results From the Fracture Intervention Trial Long-Term Extension, Ensrud K et al. J Bone Miner Res 2004;19:1259 –1269

5. Offset of effect on bone resorption after 7 years of Risedronate therapy, Hannon et al. Bone 2009; 44: S238

Tolerability of generic alendronate vs branded bisphosphonates:

6. Disintegration/dissolution profiles of copies of Fosamax (alendronate)
Epstein S et al. CMRO 2003; 19(8)781-789.

7. Disintegration and Esophageal Irritation Profiles of Alendronate Formulations: Implications for Clinical Safety and Efficacy
Epstein S et al. Journal of Applied Research 2005; 5(2)253-265.

8. In vitro disintegration and dissolution studies of once weekly copies of alendronate sodium tablets (70 mg) and in vivo implications, Dansereau R et al. CMRO 2008; 24(4) 1137-1145

9. In vitro disintegration studies of weekly generic alendronate sodium tablets (70 mg) available in the USA, Dansereau R et al. CMRO 2009; 25 (2), 449–452

10. In vitro comparison of oesophageal adhesiveness of alendronate generics vs branded alendronate, Shakweh M et al. Eur J Pharm Sc 2007. 31: 262-270

11. Oesophageal transit and *in vivo* disintegration of branded risedronate vs 2 generic alendronate formulations, Perkins et al – Clin Ther. 2008; 30: 834-844.

12. Differences in persistence, safety and efficacy of generic and original branded once weekly bisphosphonates in patients with postmenopausal osteoporosis: 1-year results of a retrospective patient chart review analysis, Ringe J and Moller G – Rheumatol Int 2009 - DOI 10.1007/s00296-009-0940-5

13. Treatment Discontinuation Due to Gastrointestinal Adverse Events and Decreased Bone Mineral Density in Patients Switched from Branded Alendronate to Generic Alendronate, Grima D, et al. J Bone Miner Res 2008;23(Suppl 1)

14. The Effect Of Switching Patients From Risedronate To Alendronate On The Risk Of Upper Gastrointestinal (Gi) Adverse Events After The Introduction Of Generic Alendronate Products In The UK, Ralston S, et al. Osteoporos Int (2009) 20:163–186

15. Switching From Branded Alendronate Or Risedronate To Generic Alendronate: Effect On Persistence With Bisphosphonate Therapy In Germany, Ziller V, *et al. Bone* 2009; 44: S Abstract

16. Differences in persistence among different weekly oral bisphosphonate medications Sheehy et al . Osteoporos Int 2008 DOI 10.1007/s00198-008-0795-8

Effect of persistence and compliance on fracture reduction

17. Impact of compliance with osteoporosis therapy on fracture rates in actual practice, Caro JJ et al, Osteoporosis Int, 2004, 15, 1003-1008

18. Effect of adherence on lifetime fractures in osteoporotic women treated with daily and weekly bisphosphonates, Danese MD, Badamgarav E, Bauer DC, J Bone Miner Res. 2009 Nov;24(11):1819-26.

19. Impact of noncompliance with alendronate and risedronate on the incidence of nonvertebral osteoporotic fractures in elderly women, Blouin et al . Br J Clin Pharmacol 2008 DOI:10.1111/j.1365-2125.2008.03178.x

20. Compliance and persistence with bisphosphonate dosing regimens among women with postmenopausal osteoporosis, Cramer JA. Amonkar MM. Hebborn A. Altman R, Current Medical Research & Opinion. 21, 1453-60, 2005

21. Sambrook PN, Chen J, Simpson JM, March L, Impact of Adverse News Media on Prescriptions for Osteoporosis: Effect on Fractures and Mortality, Med J Aust, submitted

Less Frequent Regimens: Impact on Compliance, Persistence

22. Patient preference for once monthly ibandronate versus once-weekly alendronate in a randomized, openlabel, cross-over trial: the Boniva Alendronate Trial in Osteoporosis (BALTO) Emkey R et al. Curr Med Res Opin 2005; 21:1895–1903.

23. Treatment preference for monthly oral ibandronate and weekly oral alendronate in women with postmenopausal osteoporosis: A randomized, crossover study (BALTO II), Hadji P et al. Joint Bone Spine 2008; 75:303–310.

24. A Future Less Fragile – Access Economics Report, February 2010.