Australian & New Zealand
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Senator Rachel Siewert, Chair, Senate Community Affairs References Committee – Therapeutic Groups Inquiry

Dear Senator Siewert,

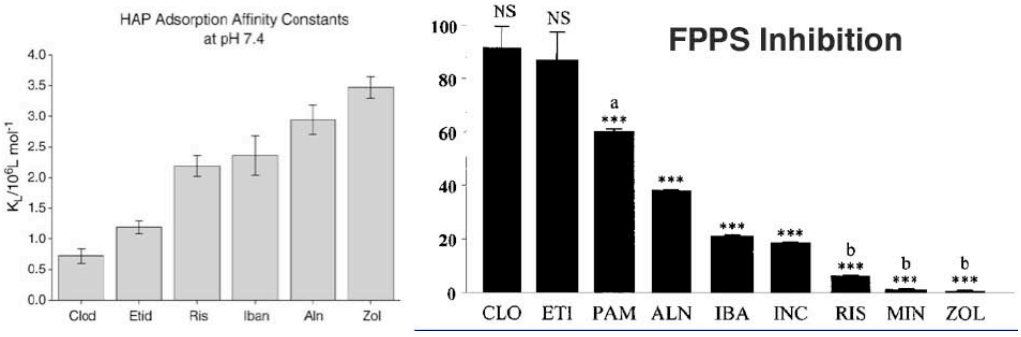
We are writing in our capacity as the Therapeutics Committee of the Australian and New Zealand Bone and Mineral Society (ANZBMS) to urge the Community Affairs References Committee to consider reversing the proposal by the PBAC to create a new Therapeutics group ie the Bisphosphonates. These medications are the most commonly prescribed therapy for Osteoporosis – a disease in the top 10 of Australia's Health Initiatives. The PBAC propose that all oral Bisphosphonates be considered as equivalent to generic alendronate and therefore interchangeable at an individual patient level.

In practice, such interchangeability would mean 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 once weekly or Actonel once monthly, with or with out calcium and/or vitamin D. The proposal also assumes it will make no practical difference to the patient or their subsequent outcome.

The view of the Society is that this is not consistent with the prevailing scientific evidence. There are substantial differences between alendronate and risedronate as well as emerging evidence of differences between generic alendronate and branded Fosamax and Actonel, which could impact on their safety, compliance, persistence and most importantly fracture outcomes. We say that for a number of reasons:

1. Bisphosphonates are not all the same.

There are well documented differences in bisphosphonate pharmacology such as differences in potency in inhibition of a key enzyme (FPPS) and binding to bone mineral (see Figure below). These differences are now thought to translate into differences in terms of absorption and hence entry into bone, differences in time to onset of anti-fracture efficacy and time to achieve offset of effects after drug cessation (1-5). The latter is particularly important given the prolonged retention of bisphosphonates in bone.



2. Adverse events and poorer compliance

There is beginning to emerge evidence that generic alendronate is associated with altered dissolution times in the gastrointestinal tract (6-11) and increased gastrointestinal side effects compared to non - generic bisphosphonates (12-16). Although this area clearly requires further study, if substantiated in larger independent trials it would lead to poorer compliance by patients and more fractures (12, 13) and therefore overall increased health costs.

The Drug Utilization Subcomittee (DUSC) wrote to ANZBMS earlier this year asking for our views on why antiresorptive therapies are currently under-prescribed in Australia. ANZBMS outlined a number of reasons for this and the Society believes the current proposal will may exacerbate this problem due to poorer tolerability as well as poorer efficacy (in relation to concomitant calcium and vitamin D supplementation, as discussed below) and may well to lead to overall increased costs to the Government due to more fractures (17-20).

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

Fosamax comes with Vitamin D supplementation plus optional Calcium, Actonel also comes with both Vitamin D supplementation plus Calcium, at no additional cost to the PBS. In this context it is important to note that the pivotal fracture trials with bisphosphonates were all done with concomitant vitamin D and calcium supplementation. The number of patients taking concomitant calcium and vitamin D became a real issue for patients after the previous Government withdrew Calcium supplementation from the PBS a few years ago. Accordingly the provision of calcium and vitamin D by industry without additional cost to patients was welcomed by the Society. With the new proposal many patients will forego concomitant calcium and vitamin D due to cost. Pensioners, in particular, are likely to be disadvantaged by the additional cost of purchasing vitamin D and calcium supplements raising issues of equity of access. Furthermore, although most patients will benefit from supplementation with calcium and vitamin D, some only need calcium supplements, while others may require vitamin D to correct their vitamin D deficiency. The non-generic preparations currently available in Australia allow for differential supplementation of calcium or vitamin D or both in combination with a bisphosphonate.

3. Constraints on administration regimens

Better compliance and persistence with bisphosphonates is associated with reduced fractures. Better compliance and persistence is seen with less frequent dosing (22, 23), eg weekly vs daily, and now once monthly oral administration. There is no once monthly formulation of generic alendronate. This flexibility in dosing schedules is a real advantage for many patients.

4. Risedronate is approved for treatment of steroid osteoporosis, alendronate is not.

How will this problem be addressed? Presumably a non approved drug could not be supplied by pharmacists.

To summarise, the view of the Society is that this proposal is economically driven, not based on medical science or patient concern. The PBAC has advised us that industry is to blame if patients have to pay a differential for branded non – generic product compared to generic alendronate. We are not concerned who is to blame, government or industry. Our practical concern as treating clinicians is that if a therapeutic group for bisphosphonates is created, there will be inequity of access that is likely to lead to poorer compliance, more fractures and increased health costs overall. As specialists in the treatment of Osteoporosis with first hand experience of the therapies available, we are concerned at the lack of

consultation in the development of this economically driven proposal and urge the Senate References Affairs Committee reverse the recommendation for this proposal. We would be happy to meet with the Senate Affairs References Committee to further outline our concerns.

Yours sincerely,

Prof Philip Sambrook

Prof Ego Seeman

A/Prof Peter Nash

A/Prof Mark Kotowicz

Prof Markus Seibel

Prof Rebecca Mason

Members of the Therapeutics Subcommittee, ANZBMS

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/s00198-0070540-8
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) 11371145
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.