29th August 2006

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Dear Dr Longson,

Health Technology Appraisals

Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women

Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women

Merck Sharp & Dohme Ltd. (MSD) would like to thank you for the opportunity to comment on the additional analyses which were prepared by ScHARR for the above appraisals. After reading the documents MSD is of the opinion that the additional work that has been done is generally of a high quality and should assist the Appraisal Committee in preparing valuable guidance for the NHS.

We do, however, have some comments on the new cost-effectiveness analyses and the discussion of adverse events seen in bisphosphonates which we would like to share with you; please find these below. In the interests of clarity we have separated the comments into those relating to each new document.

Analyses of the cost-effectiveness of pooled alendronate and risedronate, compared with strontium ranelate, raloxifene, etidronate and teriparatide.

- **By pooling the efficacy of alendronate and risedronate a hypothetical profile is created, representing a drug that does not exist and which underestimates the efficacy of alendronate alone**

The decision to pool the efficacy of alendronate and risedronate has not been justified by any scientific rationale. Alendronate and risedronate are two totally different bisphosphonates and their effects have been shown to be different in randomised controlled trials; there are in fact head-to-head trials showing differences in their respective efficacies (the FACT studies[1]). Also, by pooling the efficacy of alendronate and risedronate, a hypothetical profile has been formed which does not exist in reality.

As alendronate alone has a greater efficacy in reducing the risk of fractures than the pooled hypothetical profile and has a cheaper acquisition cost, it follows that the cost-effectiveness of alendronate alone should be superior to the hypothetical profile of alendronate and risedronate pooled together. Thus, decisions based on the cost-effectiveness of this hypothetical pooled profile may deprive patients in whom alendronate could be a cost-effective treatment for their osteoporosis.

[1] J Clin Endocrin Metab. First published April 24, 2006 as doi:10.1210/jc.2005-2602

It is a particular worry that the document states that etidronate alone is more cost-effective than the pooled profile, and by implication both alendronate and risedronate, in some cases. We assume that the decision to pool alendronate and risedronate was taken to create a hypothetical profile to represent the bisphosphonate class. If so then consequent comparison with another bisphosphonate is confusing, and it is unclear to us why this has been done.

- **GI side effects assumed for the alendronate and risedronate pooled data are based on a study of etidronate**

In this economic evaluation it was assumed that alendronate and risedronate would have GI side-effect problems, and that patients on these two drugs would require medical care in the form of GP visits and medications (H2 receptor antagonists or PPIs). Average medical costs (£4.50/patient treated for 5 years) and utility losses (0.0013-0.0016/patients treated for 5 years) were assigned due to such side-effects to every alendronate or risedroante user. This assumption was made based on the study by van Staa et al.[2] which was an observational study of upper GI adverse events with cyclical etidronate.

However, in this evaluation etidronate was assessed separately from the pooled analysis of alendronate and risedronate. It follows that it would be logical to apply this observation of GI events to etidronate patients only in this economic model, and not extrapolate it to patients taking alendronate or risedronate. Furthermore it has been observed in randomised controlled trials that there was no difference in GI events between alendronate and placebo.[3] The assumption that patients taking alendronate would be requiring medical care is therefore not substantiated and is in fact contrary to available evidence.

- **The option of treating patients who have a fracture without performing a bone mineral density measurement was not evaluated**

This economic evaluation did not evaluate the option of treating patients with fracture without doing a bone mineral density (BMD) measurement. Klotzbuecher et al.[4] showed that the risk of subsequent fracture is higher for patients with an existing fracture. Also many trials have shown that treatment with bisphosphonates is effective regardless of BMD status if the patient had already had a fracture (FIT fracture arm). This is particularly relevant when considering patients with additional risk factors including the high age group. Initiation of treatment for patients with existing fracture may prove to be a cost-effective option and may avoid wider use of BMD scans, thereby leading to more prudent utilisation of healthcare resources.

- **The beneficial effects of alendronate have been underestimated**

In this economic evaluation it was assumed that 50% of patients who would not comply with bisphosphonate therapy would be on a bisphosphonate for only 3 months and would not therefore receive any health gain (Page 5). While this is a very crude approximation, it is also a very conservative assumption in terms of not allowing any health benefits for these patients. In randomised controlled trials it was observed that alendronate provided efficacy in terms of BMD gain and bone chemical marker reduction quite early. Therefore, the evidence would suggest that health benefits should be assigned to patients who did not continue to take alendronate for a full 5 years.

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[2] van Staa et al., Am J Med, 1997; 103:462-467
[3] Greenspan et al. Annals of Internal Medicine 21-5-2002; 136 742-746
[4] Klotzbuecher et al. Journal of Bone and Mineral Research. April 2000:15:721-739

Adverse effects associated with oral alendronate, etidronate or risedronate therapy.

- **Head-to-head placebo-controlled studies suggest that there is no difference between weekly formulations of alendronate and risedronate in terms of upper gastrointestinal adverse events.**

The FACT studies [1] (Fosamax (alendronate) Actonel (risedronate) Comparison Trial) compared changes in bone mineral density (BMD), bone turnover and upper gastrointestional tolerability in women with postmenopausal osteoporosis who were taking once-weekly alendronate 70 mg or once-weekly risedronate 35mg. The study results showed that "no differences were seen in occurrence or discontinuations due to upper gastrointestinal adverse events." [1]

However, the report compiled by ScHARR seems to suggest that alendronate has a relatively good reported tolerability due to bias. Page vi states; "In randomised trials of effectiveness, the incidence of gastrointestinal adverse events is similar in the bisphosphonate and placebo arms. Although for alendronate this may be attributed, at least in part, to the exclusion from those trials of patients with a history of upper gastrointestinal disease, this is not true of the risedronate trials."

This is an erroneous statement which we are grateful to have the opportunity to correct. The alendronate trials in question excluded patients with **active untreated** gastrointestinal disease, but allowed patients with prior gastrointestinal disease or even those with a condition such as gastro esophageal reflux disease that was controlled on medication into most Phase III and beyond studies.[5] It should be noted that when the background disease histories of patients of phase III studies in both alendronate and risedronate is compared the background upper gastrointestinal disease is equally high in both.

- **While upper gastrointestinal adverse events are a feature of bisphosphonates, these conditions are relatively common in osteoporotic patients regardless of bisphosphonate treatment.**

One of the studies considered by ScHARR [6] showed that patients who were bisphosphonate-intolerant based on their own marketed use of alendronate did have a relatively high incidence of upper GI AEs. However, the incidence was just as high in the group who received blinded placebo tablets as it was in those who took oral alendronate. We would therefore endorse the following statement which appears on page vi of the ScHARR document; "It is plausible that the high level of reporting of gastrointestinal adverse events both in patients taking oral bisphosphonates in real life and in the placebo arms of the clinical trials may be partly due to a heightened awareness of the potential for gastrointestinal adverse events with such medication."

Thank you once again for allowing us to comment on the additional work. I trust that we have made our thoughts clear, but should you have any queries or wish to discuss this in more detail please do not hesitate to contact

Yours sincerely,

[5] Bauer DC, Black D, Ensrud K, et al. Upper gastrointestinal tract safety profile of alendronate. Arch Intern Med 2000;160:517-25.

[6] Miller, P. D., Woodson, G, et al. Rechallenge of patients who had discontinued alendronate therapy because of upper gastrointestinal symptoms. Clinical Therapeutics 2000; 22 1433-1442