21st October 2005

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Dear Dr Longson

Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary and 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 ACDs for the above Technology Appraisals, as well as the assessment report. MSD is of the view that the recommendations are of a high quality and generally reflect best clinical practice in the UK. However, we would like to bring the following to the attention of the Appraisal Committee:

The Appraisal Consultation Documents

- **Primary prevention: Recommendations for identification strategy and treatment in women aged over 70 do not reflect Appraisal Committee's analysis on cost-effectiveness**

Sections 4.2.23 and 4.2.25 state the criteria for selection of patient groups for whom strategy for identification and treatment is cost-effective, yet these are not reflected in the actual recommendations.

- **Primary and secondary prevention: Alendronate should be differentiated from other bisphosphonates based on superior clinical and cost effectiveness**

This superiority has been recognised by the ACD in section 4.2.10, as well as being stated repeatedly in the addendum report.

The Assessment Report

- **Assumption of a 5-year period during which therapy effect linearly goes down to 0.**

Alendronate demonstrated residual effect on bone mineral density and reduction in bone turnover even after discontinuation of therapy.

Additional information supporting these statements is provided in the appendix to this letter. However, should you wish to discuss this in more detail please do not hesitate to contact

Yours sincerely

Medical Director

Appendix

i. NICE recommendation for primary prevention is not reflective of Appraisal Committee's findings on cost-effectiveness

- It is stated in the evaluation report that at age 70 years and above, the strategy for identification and treatment for primary prevention of osteoporotic fractures starts becoming cost-effective (table 11, 12 and 13) regardless of whether RCP or WHO strategy is used.[1] In the ACD for primary prevention of osteoporotic fragility fractures in postmenopausal women, section 4.2.23 states that "In women under the age of 70, identification based on the RCP and on the WHO algorithm-based approaches resulted in negative net benefits, that is were not cost-effective, assuming a maximum acceptable ICER of £20,000 for an additional QALY. At age 70 and above both approaches resulted in a positive net benefit (i.e. the benefits of the identification and treatment strategy outweighed the costs)."[2] Further the section 4.2.25 is as followed: "In women over the age of 70 the following approach led to the highest net benefit.

    - Women aged 70–74, who have at least one risk factor, receive DXA scanning, and treatment at or below T-scores of –2.8, –2.3 or –1.7 when one, two or three risk factors are present, respectively.

    - Women aged 75–79 with three risk factors are treated without DXA scanning. All other women aged 75–79 receive DXA scanning, and treatment at or below T-scores of –3, –2.3 or –1.5 when zero, one or two risk factors are present, respectively.

    - Women above the age of 80 with two or more risk factors are treated without DXA scanning. All other women over the age of 80 receive DXA scanning and treatment at or below T-scores of –2.3 or –1.5 when zero or one risk factor is present, respectively."

    While such findings were from the base case scenario, the recommendations from NICE in section 1.1 do not reflect this. Instead section 4.3.13 states that the committee noted that cost-effectiveness was sensitive to compliance, and that compliance with bisphosphonates was low. It appears that the sensitivity of cost-effectiveness to varying degrees of compliance was only tested in the sensitivity analysis. So far no study has been conducted to estimate the exact relationship between the varying degree of compliance with bisphosphonates and relevant efficacy. Further, there is plenty of evidences that compliance with bisphosphonates is higher than 50% (Mean Possession Ratio>50%).[3,4,5]Therefore such consideration of impact on compliance on clinical effectiveness and cost-effectiveness is not evidence-based. Instead MSD recommend that

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[1] Overview: The clinical effectiveness and cost effectiveness of technologies for the prevention of osteoporotic fragility fractures in postmenopausal women. National Institue for Health and Clinical Excellence, Septtember 22, 2005. Page 27-28.

[2] Final Appraisal consulting document: Alendroante, etidronate, risedronate, raloxifene, and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women. September 22, 2005.

[3] Cramer JA, Amonkar MM, Hebborn et al."Does dosing regimenn impact persistence with bisphosphonate therapy among postmenopausal osteoporotic women? Journal of Bone Mineral Research. 2004; 19(Suppl 1): S448.

[4] Cooper C, Sen SS, Zhang Q, et al. "Persistency with osteoporotic medications in the United Kingdom." Annals of the Rheumatic Diseases. 2002; 61(S1):240;

[5] Recker R, Gallagher R, Amonkar M, et al. Journal of Bone Mineral Research. 2004; 19(Suppl 1): S172.

the committee consider the base case scenario where the data used is more robustly based on current evidences.

ii. All therapies were assumed to have 5 years of therapy followed by a 5-year period during which therapy effect linearly goes down to 0, whereas Alendronate has clear evidence for 10 years.

- In long term studies, alendronate demonstrated residual effect on bone mineral density and reduction in bone turnover even after discontinuation of therapy. The assumption of a 5 year set-off time as used in the appraisal model, when the treatment effect returns to zero for all interventions, is not therefore an appropriate reflection of the effect of alendronate, and does not give due credit to alendronate for its BMD increasing effect. A two-year period after therapy discontinuation, during which the therapy effect remains the same, would be a more accurate reflection.
- Across all therapies analysed, alendronate has most evidence from trials beyond 5 years. For this reason, the Assessment Report approach significantly understates the clinical effectiveness of alendronate while possibly overestimating the effect of other therapies.

iii. Alendronate should be differentiated from other bisphosphonates for the primary and secondary prevention of osteoporotic fragility fractures based on superior clinical and cost effectiveness

- MSD has consistently demonstrated alendronate's superior clinical and cost effectiveness for the primary prevention of osteoporotic fragility fractures in post menopausal women.[6]
- In the addendum report issued on July 4, 2005, it has been reported on Figure 1 through 7 and Table 2 through 8, that alendronate is the most cost-effective treatment for primary prevention of osteoporotic fractures. Similarly figure 8, 9 and 10 on page 12 and 13 of the addendum to assessment report suggest that alendronate was the most effective intervention for secondary prevention of osteoporotic fractures.[7]
- Further, this superiority has been recognised by the team at appraisal team on page 22 section 4.2.10 of the ACD: "Alendronate is taken as a proxy of the bisphosphonates because the data for alendroante generally provide the best case in terms of cost-effectiveness."[8] Also it was stated in relation to strontium ranelate: *"Alendronate has been chosen as the drug to be used in evaluating identification strategies since it has better mid-point efficacies than strontium ranelate and is also cheaper"*[9]
- MSD urges the Appraisal Committee to recognise alendronate's superiority and differentiate between the bisphosphonates in the primary and secondary prevention ACD.

[6] MSD response to Assessment Report produced by ScHARR for the Clinical and Cost Effectiveness of technologies for the Primary Prevention of Osteoporotic Fragility Fractures in Postmenopausal Women, 31.3.05

[7] The clinical and effectiveness and cost effectiveness of technolies for the primary prevention of osteoporotic fragility fractures in postmenopausal women. Addendum to Assessment Report. July 4, 2005.

[8] Final ACD Osteoporosis secondary prevention, September 22, 2005

[9] The clinical effectiveness and cost effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in post menopausal women – Assessment Report July 2005, pg 97