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Dear Dr Longson

The clinical effectiveness and cost effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in post menopausal women

Thank you for the opportunity to comment on the Assessment Report for the above appraisal and the Economic Addendum for the appraisal of the clinical effectiveness and cost effectiveness of technologies for the primary prevention of osteoporotic fragility fractures in post menopausal women.

Please find below comments from Merck Sharp & Dohme Ltd (MSD). As requested, we have read these documents alongside each other and have separated our comments into those related to primary prevention and those related to secondary prevention.

We would urge the Appraisal Committee at NICE to take the following points into consideration when preparing Appraisal Consultation Documents (ACDs) for primary and secondary prevention for all referred technologies:

Primary Prevention

Alendronate should be differentiated from other bisphosphonates for the primary 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.[1]
- In the economic addendum, Figures 1-7 and Tables 2-8, demonstrate alendronate is the most cost-effective treatment for primary prevention of osteoporotic fractures.
- Further, this superiority has been recognised by the team at ScHARR 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"* [2] and as presented in Tables 48-54. Comparing results of cost-effectiveness analysis of strontium ranelate (Tables 41-47) and alendronate (Tables 48-54), the report concluded that strontium ranelate is not as cost-effective as alendronate.

[1] 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

[2] 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

- MSD urges the Appraisal Committee to recognise alendronate's superiority and differentiate between the bisphosphonates in the primary prevention ACD.

Secondary Prevention

Alendronate should be differentiated from other bisphosphonates for the 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 secondary prevention of osteoporotic fragility fractures in post menopausal women.[3]
- The Economic Addendum further showed that alendronate is the most cost-effective therapy for secondary prevention of osteoporotic fractures (Figures 1-7), particularly when the appraisal is focused on its original objective of assessing technologies for prevention of secondary osteoporotic fractures.
- This superiority has been recognised by the team at ScHARR in relation to strontium ranelate, in particular, the fact that alendronate was chosen as the bisphosphonate comparator in the economic appraisal (pg 52) and then subsequently demonstrated clinical and cost effectiveneness in several sections of the Assessment Report:
    - *"The results of the probabilistic sensitivity analysis using efficacy data from randomised controlled trials suggest that [strontium ranelate] is not as cost effective as alendronate"* (pg 10)
    - *"..the same graph is shown for alendronate, which is seen to be more cost-effective at given risks than strontium ranelate"*. (pg 67)
    - *"It is seen that based on our results, alendronate appears more cost effective than strontium ranelate"*. (pg 68)
    - *"As expected, since alendronate has better mid point efficacy at all sites, and has a lower acquisition price, it is optimal on substantially more occasions than strontium ranelate"*. (pg 76)

In addition to the points above, MSD would like to add the following more general comments that we believe should be taken into consideration when determining the contents of the new ACD's for primary and secondary prevention:

Vitamin D adequacy:

- Guidance 87 (Osteoporosis: Secondary Prevention) covered the treatment of postmenopausal women who have normal calcium levels and/or vitamin D levels, and recommended that *"Unless clinicians are confident that women who receive osteoporosis treatment have an adequate calcium intake and are vitamin D replete, calcium and/or vitamin D supplementation should be provided"*.
- MSD urges the Appraisal Committee to ensure this recommendation is transferred to the new ACD because:
    - Vitamin D inadequacy is widespread in postmenopausal women[4]
    - The rate of use of vitamin D supplementation remains very low in osteoporotic population[5]

[3] MSD response to Final Appraisal Determination (FAD) for the secondary prevention of osteoporotic fractures in postmenopausal women, 9.8.04, MSD response to Appraisal Consultation Document (ACD) for the secondary prevention of osteoporotic fractures in postmenopausal women, 20.5.04

[4] See Appendix point 1 for supporting evidence

[5] See Appendix point 2 for supporting evidence

Should you require any additional information please do not hesitate to contact.

Yours sincerely

Dr John Young
Medical Director

APPENDIX

1. Vitamin D inadequacy is widespread in postmenopausal women

- Serum levels of the metabolite 25-hydroxyvitamin D, 25(OH)D, are used to measure vitamin D adequacy status. In the medical literature at present there is no internationally agreed consensus on what should constitute a diagnostic serum level for vitamin D insufficiency. A common approach is to consider the level of 25(OH)D at which parathyroid hormone (PTH) is maximally suppressed, as PTH is known to increase resorption of bone and thus reduce bone density. PTH levels have been shown to rise as vitamin D levels fall below a certain level. Estimates of 25(OH)D levels required for PTH suppression have varied from 30 to 99 nmol/L, although there has been a clustering of estimates around the 75-80 nmol/L range.[1-7]
- Work presented in 2005 used a cut-off for vitamin D inadequacy of <30ng/ml (equivalent to approximately <75nmol/L), and showed that in Europe, 51.9% of postmenopausal women with osteoporosis had inadequate vitamin D levels.[8]
- Separate work in Glasgow has revealed in a retrospective audit that 97.8% of patients aged 50 or over who had sustained a hip fracture had 25(OH)D levels less than 70 nmol/L.[9] Prospective work by the same team showed that 82.0% of patients over 50 presenting with a clinical non-vertebral fracture had levels below 70 nmol/L.[9]
- Higher vitamin D levels also allow increased absorption of calcium from the diet. For example, calcium absorption has been shown to be 65% greater at serum 25(OH)D levels averaging 86.5 nmol/L than at levels averaging 50 nmol/L.[10]

2. The rate of use of vitamin D supplementation remains very low in osteoporotic population

- A database analysis using combined data from the 2002 and 2003 National Health and Wellness Surveys (NHWS) in France, Germany and the UK indicated that fewer than one in five women with osteoporosis are taking a vitamin D supplement. Even among high risk patients with a fracture history, only 1 out of 5 patients used vitamin D supplementation[11].
- A follow-up survey among the 100,697 patients from the National Osteoporosis Risk Assessment (NORA) study evaluated the utilization of vitamin D supplements and factors related to its use in women with osteoporosis, recent fracture or on osteoporosis treatment[12]

3. Teriparatide lacks evidence of reduction of hip fracture risk

- As indicated on table 1, page 3 of the Addendum, the confidence interval for relative risk for hip fracture for Teriparatide is very wide and includes 1 (0.09, 2.73) which indicates that there is no defined effect. Considering this it seems appropriate that no hip fracture risk reduction be included in the cost-effectiveness analysis of teriparatide.

4. **Raloxifene is not indicated for treatment of breast cancer which is also not the focus of the original scope of this appraisal**

- Figures 2-7 of the Addendum indicate raloxifene's cost-effectiveness is extremely dependent on breast cancer benefits. In fact, raloxifene's cost-effectiveness deteriorates with increase in risk of fracture. This is explained in the report by possible existence of inverse relationship between BMD and breast cancer risk. This may indicate that raloxifene's cost-effectiveness is very much driven by breast cancer benefits.
- Considering raloxifene is not indicated for breast cancer therapy and the focus of this appraisal is prevention of osteoporotic fractures, it is inappropriate to include breast cancer benefits of raloxifene into the cost-effectiveness analysis for osteoporosis.

5. **Strontium ranelate is associated with significant ($p<0.05$) higher risks of VTE, diarrhoea, loose stools and allergic dermatitis; all have economic implications**

- The Strontium Ranelate Assessment Report (pg 9, 'Executive Summary' and Table 16) indicates that patients with strontium ranelate had significantly higher risk of venous thromboembolism (RR=-1.42, 95% CI: 1.02 to1.98).
- Further, Table 16 indicates patients on Strontium Ranelate also had significantly higher risk of nausea (RR=1.55, $p<0.0001$), diarrhoea (RR=1.41, $p=0.0008$), loose stools (RR=5.94, $p<0.0001$) and allergic dermatitis (RR=1.81, $p=0.04$).
- Evidence based medicine would suggest incorporation of such side-effect in the economic evaluation. Considering the current structure of the model, such events can not be incorporated in the model. Nonetheless, they are associated with substantial economic impact. MSD suggests that future appraisals should consider incorporation of such events into the economic analysis.

6. **Hip fracture risk reduction with strontium ranelate should only be included the economic analysis if its confidence interval does not include 1**

- From Table 26, it seems a point estimate was used for relative risk of hip fracture with strontium ranelate. Since this information is not disclosed, it is difficult to know what effect it had on the economic model. However, incorporation of this point estimate into the economic model is only justified if the confidence interval does not include unity.

7. **Inappropriate use of 10 year time horizon**

- The assessment team used a 10-year time horizon for Strontium Ranelate, however, the technology does not have data for 10 years. This fact undermines the evidence spanning 10 years that exists for agents like alendronate.

APPENDIX REFERENCES

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