Comments on Health Technology Appraisal: The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women: Professor Juliet Compston and Dr Peter Selby

In general the report reads well and the addition of clinical risk factors to BMD in assessing fracture risk represents a significant advance in terms of the strategies for identification. However, a number of points require attention. As requested, these are divided according to the three sections of the appraisal document.

The clinical effectiveness and cost-effectiveness of strontium ranelate in the prevention of osteoporotic fragility fractures in postmenopausal women

1. Hierarchical categorisation of interventions is hard to justify in the absence of direct comparator studies. It is claimed that alendronate is more cost-effective than strontium ranelate; although the latter is slightly more expensive, there are no significant differences in efficacy between the two agents and no direct comparator studies. Are there significant differences in the acceptability curves (Fig 9 and 10)? If not, this weakens still further claims for distinguishing the two treatments on the basis of cost-effectiveness.

2. The terminology "first- and second-line" with respect to strontium ranelate and alendronate is not appropriate in the context of a judgement based solely on cost-effectiveness. The positioning of these (and other agents) in the prevention of osteoporotic fractures requires consideration of other factors and should be the remit of the Guidelines Development Group.

Clinical effectiveness and cost-effectiveness of technologies for the primary prevention of osteoporotic fragility fractures in postmenopausal women

1. A major concern relates to the discrepancy between the cost-effective fracture probability intervention thresholds in this document and those previously determined and reported by Kanis et al. These discrepancies will lead to confusion and undermine the credibility of the NICE appraisal. Expression in the NICE analysis of fracture risk as an annual risk rather than 10-year fracture probability (as in the WHO report) will add further to the confusion, since the two sets of figures cannot be directly compared. Nevertheless, it is clear that the intervention thresholds differ by an order of magnitude; thus in the NICE appraisal, the intervention threshold is typically between 2 and 4% annual fracture risk whereas the WHO figures range from a 10-yr (hip) fracture probability of 1.1% at age 50 years to 9% at age 85 yrs. Both sets of figures are based on a cost/QALY of £30k.

2. A second concern relates to the omission of identification strategies in women aged under 70 years (assuming the £20,000 cost/QALY threshold). Some of the possible explanations as to why this model is unfavourable to younger women, as compared with that of Kanis et al, are discussed on page 111. The underestimation in the NICE analysis of long-term disutility in younger women sustaining a fracture is likely to be an important factor and should surely be addressed. In addition, the assumption that BMD values are

not affected by the number of clinical risk factors is counter-intuitive and disadvantages younger women.

3. Although the consideration in this report of individual risk clinical factors in prediction of fracture risk is welcome, the presentation in Tables 27-40 and 41-54 is too complex to be useful in clinical practice and does not include all possible combinations of risk factors. Some simplification of approach would be helpful, for example giving individual scores to each risk factor, recognising that scores may be age-dependent and differ for different fractures. The report should acknowledge that thresholds are approximations and will need to be guided by clinical information.

4. The omission of BMI in the model is unfortunate, since this is an important risk factor for fracture, particularly hip fracture, and would be valuable in targeting women more accurately for BMD measurement. The argument that the correlation between BMI and BMD in the Holt database was low lacks validity in the light of the strong evidence to the contrary in larger population-based cohorts and the evidence from a number of sources that below a BMI of 22kg/m^2, fracture risk is increased. An acceptable compromise would be to dichotomise BMI.

5. The assumption in the model that all women have a BMI of 26 is hard to sustain. For a woman of average height (167.6 cm or 5ft 6inches) this translates into a body weight of 72.5 kg or 11 stone 4 lb, which most would consider to be overweight.

6. In terms of identification strategies, it should be recognised that identification costs will not be uniform for all risk factors. For example, women with rheumatoid arthritis, those receiving glucocorticoid therapy, and those with fragility fracture will have GP appointments unrelated to case finding for osteoporosis and the identification costs will therefore be considerably less. As it stands, a 65 year old woman with rheumatoid arthritis who was receiving prednisolone 20 mg daily would not be either investigated or treated (assuming the 20,000k cost/QALY threshold); this reflects both the manner in which younger women are disadvantaged by the model and the overestimation of cost of identification strategies in some women.

7. In the cohorts used for this analysis, the contribution of glucocorticoid therapy to fracture risk was based on individuals who were ever users and therefore substantially underestimates the increase in fracture risk in current users, particularly those on higher doses. There is good evidence that fracture risk rises rapidly on starting glucocorticoid therapy (within the first three months) and reverts towards baseline after treatment is stopped. The algorithms must therefore incorporate higher levels of risk for a). current users and b). those on high doses of prednisolone. The same principle applies to the presence of multiple fragility fractures.

Addendum

1. In the update of the secondary prevention economic analysis the cost-effectiveness of different interventions is considered in women with a fragility fracture ± other clinical risk factors. There is no summary or discussion of the results of this section but

algorithms based on these data and presented to the Guidelines Development Group indicate that investigation and/or treatment in women with a fragility fracture who are under the age of 60 years is not cost-effective according to this model. The main reason why this reanalysis has generated more conservative cost-effectiveness figures than the initial secondary prevention appraisal is that the estimates for efficacy of different interventions have been revised. Thus in the initial appraisal, estimates of efficacy were derived solely from secondary prevention trials whereas in the reanalysis the estimates are pooled from primary and secondary prevention studies. The latter approach provides considerably lower estimates for efficacy at hip and other non-vertebral sites, so that even though the second analysis included all osteoporotic fractures (and hence would be expected to be more favourable to intervention), the end result is lower cost-effectiveness. In view of the robust database for secondary prevention, the reanalysis should be redone using estimates of efficacy derived only from secondary prevention studies, as in the initial appraisal. The different estimates (RR) are given below:

Existing appraisal on secondary prevention
Vertebral fractures 0.53
Hip fractures 0.46
Wrist fractures 0.48

Reanalysis
Vertebral fractures 0.56
Hip fractures 0.62
All non-vertebral fractures 0.81