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2nd September, 2005

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Dear Dr Longson

NICE Osteoporosis Guideline Development Group comments on: Health Technology Assessment Report: The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in post-menopausal women.

The NICE Osteoporosis Guideline Development Group have considered the above report. The report is well constructed and addresses the important issue of treating on the basis of fracture risk rather than solely on the T-score for BMD. A significant amount of work has been done however, there are still outstanding issues that require addressing. These are as listed below.

1. It is not possible at present to compare the results of this analysis with cost-effectiveness thresholds previously determined by Kanis et al. Whereas direct comparisons may not be possible (as discussed in p110), the analysis of Kanis expresses intervention thresholds as 10-year hip fracture probabilities. It is essential that the report gives 10-year hip fracture probabilities otherwise the credibility of the analyses will be undermined.

2. The cost-effectiveness of identification strategies depends critically upon the acquisition costs. Identification costs will not be uniform for all risk factors. For women with a prior fracture, this is reasonably set at 0, since patients will be self evident. The same situation also pertains to women with rheumatoid arthritis or women taking glucocorticoids. Failure to recognise this disadvantages this segment of the population, particularly in younger individuals.

3. The hierarchical categorisation of interventions is concerning in the absence of direct comparator studies. It is claimed that alendronate is more cost-effective than strontium. There are slightly higher drug costs, but no significant differences in efficacy between the two agents and no direct comparator studies. It is unclear whether there are significant differences in the acceptability curves (Fig 9 and

10)?. If not, this weakens still further claims for first time treatments. The terminology “first and second-line” is not appropriate in the context of a judgement based solely on cost-effectiveness. This requires consideration of other factors and is the remit of the GDG.

4. The neglect of BMI as a risk indicator is a serious omission. The argument that the correlation between BMI and BMD is low is inadequate, since it is only at BMI’s of 22 Kg/m^2 or less that the risk is increased. If the complexity of the mathematics is too onerous, then dichotomisation of BMI would be an alternative approach.

5. The setting of a BMI at 26 Kg/m^2 seems inappropriate given that this is within the range of overweight.

6. The ratio of other femoral and pelvic fractures to hip fracture is undertaken in a different way than the ratio for other osteoporotic fractures. It would be more appropriate to use a common methodology such as the Swedish database.

7. Cost-effectiveness calculations are dependent on the mortality assumptions after hip fracture (Table 6, page 28). These appear to be very conservative compared with published estimates.

8. As acknowledged in the discussion (p110), the proportion of patients entering nursing homes after hip fracture may be seriously underestimated. Also, the assumption that fractures other than those at the femur or pelvis never result in nursing home admissions is not credible. Both these factors will have a marked effect on cost-effectiveness.

9. It is unclear whether table 4 (p25) includes fractures of the humeral shaft. If not, these should be included.

10. QALY’s appear to be handled over a lifetime (p65), but not costs. The rationale for this apparent inconsistency needs to be described.

11. There seems to be a disparity in the description of Fig 16 and the figure itself.

12. The report needs to acknowledge that thresholds will only be approximations and will need to be guided by clinical information. This is the role of the GDG. For example, the ever-exposure to glucocorticoids will underestimate the risk of current exposure. Moreover, the risk with an average dose is less than the risk of a high dose. The same is true for many of the other risk factors such as the number of prior fractures. The implication that a women aged 60 with several fragility fractures should not be treated is inappropriate. The presentation in parts of the report, for example Tables 27-40 and 41-54, is too complex to be useful in clinical practice and needs to be simplified with accompanying explanatory text. It also does not include all possible combinations of risk factors.

13. The update of the secondary prevention economic reanalysis has generated more conservative cost-effectiveness figures than the initial secondary prevention appraisal. This is because the estimates are now pooled from primary and

secondary prevention studies resulting in lower cost-effectiveness. Reanalysis should be conducted using estimates of efficacy derived only from secondary prevention studies as in the initial appraisal.

As discussed, I understand that this letter will be circulated to the TA Committee ahead of the meeting on the 6th September. The GDG would appreciate a written response once the TA Committee have considered the issues set out within this letter. We look forward to working together in the coming weeks to produce the much needed high quality guidance to the NHS. If you have any queries regarding this letter, please contact, Acting Director of the NCC-NSC

Yours sincerely

Professor David Barlow
Chair, Guideline Development Group on behalf of the Osteoporosis Guideline Development Group

cc. Dr Mercia Page, Director, Centre for Clinical Practice NICE