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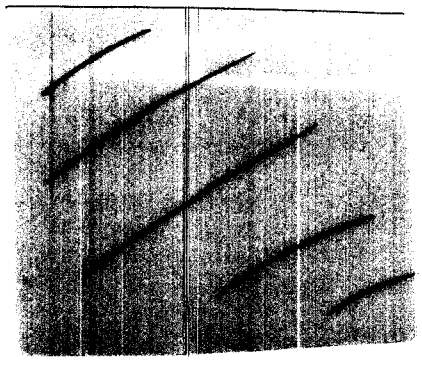
The University of Manchester



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22 April 2008

Dear Carole

Health Technology Appraisals: Primary and Secondary Prevention of Osteoporotic Fragility Fractures in Postmenopausal Women – Comments on ACDs

Thank you for asking for my comments on this proposed guidance. I will use the headings under which you have sought comments but will comment on both ACDs together unless I state otherwise.

Has all the relevant evidence been taken into account?

1. This guidance has been through so many iterations now that I believe that most of the evidence regarding clinical effectiveness has been taken into account. However there are some areas where there still seems to be insufficient note taken of the available evidence. Most important of these is the area of risk factors. The list of risk factors given by the committee is a small subset of all recognised risk factors. Also the distinction between those that work through BMD and those that are independent of BMD is much less well defined in real life than the committee appear to believe.

2. The committee are wedded to the notion that alendronate is less effective in patients with osteopenia. The evidence they cite is applicable only to the primary prevention setting as the interaction between BMD and treatment effect was seen in women selected on the basis of BMD alone. In those selected on the basis BMD and prior fracture no such interaction was noted. Para 4.1.9 in the secondary prevention ACD is therefore not appropriate.

3. The committee persist in applying an arbitrary increase in the incidence of side effects to try and capture the "unknown unknowns" they have not been able to model. This seems to be applied to all the technologies under review and it is difficult to see how it is justifiable to take the side effect profile of one drug and apply it across the board to all the other drugs under review. At the appeal we were assured that this was not applied to other agents. Paragraphs 4.3.16 and 4.3.17 respectively appear to suggest that this contrary to that assurance this has been applied across the board.

Are the summaries of the evidence and the views on resource impact and implications appropriate?

4. The committee are already aware of my concerns regarding their apparently arbitrary approach to selection of evidence and definition of inputs to the economic model. It is a

matter of regret that this approach has been continued here. In particular it would appear that the committee, without any scientific or clinical rationale, has taken the position least favourable to treatment at every opportunity. Coupled with the additional hurdle of an arbitrary increase in side effects (see 3 above) it is unsurprising that the committee has arrived at a position that is unfavourable to intervention. Along with some colleagues I have recently published an economic analysis of osteoporosis treatment using more realistic assumptions which suggests that it could be much more cost effective to treat than the committee suggest (1). As a consequence I believe it is likely that following the advice of the committee will lead to many women being denied treatment that could be offered cost effectively.

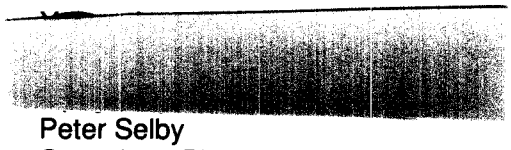
Do the recommendations constitute a suitable basis for guidance to the NHS?

In addition to the concerns I have on the validity of the assumptions on which the guidance has been based I also have several concerns about the way in which could be implemented.

5. Especially for primary prevention the guidance is far to complex to be easily used in busy clinical practice. The concept of different types of risk factor is alien to most people's understanding of the disease and the multilayered tables are very user unfriendly. Unless the treatment paradigm can be simplified or offered in more convenient form (eg simple program) then it is unlikely to be used.

6. Like many of the colleagues with whom I have discussed the proposed stepped guidance for women who are intolerant of alendronate I find it hard to see how these proposals can be meaningfully translated into clinical practice. Whilst I accept that the Institute has to give advice based on cost effectiveness it also needs to give guidance that is realistic in a clinical setting. The current proposals fail to do that and will be difficult to implement in practice. I do not see how I can easily explain to a patient who has been made ill with alendronate and is now worried about her osteoporosis and fracture risk that we cannot offer her any further treatment until she deteriorates as the alternatives are too expensive. Of course in TA87 risedronate was judged cost-effective as an alternative to alendronate. Whilst I realise that the fall in price of alendronate means that we should look to that as our first therapeutic choice I can see no explanation in the ACD as to why (in absence of any new evidence) something that was cost effective 3 years ago is no longer so.

I hope that you find these comments helpful and look forward to working with you to ensure that the Institute eventually is able to produce meaningful and useful guidance.



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1. Kanis JA, Adams J, Borgstrom F, Cooper C, Jonsson B, Preedy D, et al. The cost-effectiveness of alendronate in the management of osteoporosis. Bone 2008;42(1):4-15.

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