Appraisal Consultation Documents on technologies for the primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women

Dear Carole

Thank you for giving me the opportunity to comment on these ACDs in my capacity as a clinical specialist nominated by the Royal College of Physicians. As a result of the successful appeal against the FADs released in June 2007, I note that the scope has been increased to include risedronate, raloxifene, strontium ranelate and (for secondary prevention only) teriparatide. However, in other respects it appears that other recommendations made by the Appeal Panel have been largely ignored. The same is true of feedback that has been produced by stakeholders, patients and healthcare professionals over the past two to three years.

The economic model

As discussed in earlier responses, despite a greater than 75% fall in the price of alendronate since the original guidance for secondary prevention in 2005 and the draft guidance for primary and secondary prevention in September 2006, the recommendations for the use of this drug have remained substantially unchanged. This has been achieved by alteration of some of the model assumptions, in the absence of new evidence, so that the cost-effectiveness of alendronate has apparently remained unchanged despite the fall in its price. Furthermore, these changes to the model have had a negative impact on the cost-effectiveness of the other treatments under consideration. The changes in the model have been detailed in previous feedback and include a progressive lowering of the relative risk reduction at the hip for alendronate, reduction of the disutility associated with vertebral fracture, and the introduction of a disutility for side-effects and its arbitrary ten-fold multiplication. In addition, the cost-per-QALY threshold for primary prevention has been lowered from £30,000 to £20,000.

Two of these changes are particularly relevant to the outcome of the appeal hearing. In their concluding remarks, the Appeal Panel stated that “the two circumstances of primary and secondary prevention of osteoporotic fractures were so similar that it would be advisable if the Final Appraisal Document for secondary prevention explained more clearly why a higher incremental cost per QALY had been accepted for secondary prevention as compared to that for primary prevention”. The explanation provided in paragraph 4.3.15 does not meet these requirements. The description of the primary prevention population as “an asymptomatic group of adult patients” is an oversimplification. Many such women will be aware of their risk and be anxious about the possibility of suffering a fracture. Furthermore, if they are found to meet the criteria for treatment they will know that they have a diagnosis of osteoporosis and have a high risk of fracture.

The Appeal Panel also requested improved clarity and transparency in certain areas. One issue that was specifically raised during the appeal was the use of the 10x multiplication of the disutility for side-effects, not only for bisphosphonates but also for raloxifene or

strontium ranelate. In the current ACDs this lack of clarity remains in the case of etidronate, raloxifene, strontium ranelate and teriparatide.

Differential treatment thresholds for different treatments

In spite of the almost universal negative feedback from patients and stakeholders in response to the ACDs produced in September 2006, the Appraisal Committee has reverted to the concept of differential treatment thresholds for different interventions. The practical outcome of these is that some women who start treatment on alendronate but are unable to tolerate it have to wait for their disease to progress before they can receive another treatment. Furthermore, some women in whom alendronate is contraindicated will not be given alternative treatment despite being at high risk of fracture. Since the main second-line options, strontium ranelate and risedronate, are both effective and relatively cheap, this results in a situation that is distressing for patients and clinically unacceptable for doctors. Most seriously, it will discriminate against the disabled and the frail elderly populations in whom alendronate is most likely to be contraindicated as a result of cognitive dysfunction (and therefore inability to comply with the dosing instructions) or physical frailty. For those women who have already sustained a fracture, the fear of a further fracture is substantial and disabling and denial of treatment to such women on the grounds of a cost of around £250-300/year cannot be justified.

Notwithstanding these ethical considerations, the complexity of the recommendations for alternative interventions makes them clinically unworkable.

Inclusion of etidronate as a second-line drug

The ACD acknowledges the "weaker clinical evidence base" for etidronate and uses this as a reason for not updating the cost-effectiveness analysis for this drug. The recommendation that etidronate should be used as a second-line treatment alongside risedronate is contrary to the principle of basing recommendations on both clinical effectiveness and cost-effectiveness. There are no prospective data showing reduction in either non-vertebral or hip fractures in postmenopausal women treated with etidronate, whereas such data do exist for risedronate and strontium ranelate. In their concluding statements, the Appeal Panel reiterate the need to provide guidance on the basis of both clinical and cost-effectiveness.

Use of FRAX™ to estimate fracture probability

In recent feedback to the Appraisal Committee both the GDG and the National Osteoporosis Society recommended that consideration be given to basing recommendations about treatment on 10-year fracture probability, as in the FRAX™ algorithm, rather than T-scores, age and number of risk factors. FRAX™ is now widely available and increasingly used in clinical practice, both in the UK and in many other parts of the world. It is unfortunate that the Committee has chosen not to respond to this recommendation, since the intervention thresholds on which the recommendations in the ACDs are based cannot be translated into the 10-year fracture probability outputs generated by FRAX™ and will lead to confusion in clinical practice. According to the NICE website, an approach was made in January 2008 to obtain from the WHO access to the algorithms used in the construction of FRAX™, but it is stated in the ACDs that the

Committee did not have access to these algorithms. Clarification around this point is required, particularly in view of the recommendation of the Appeal Panel that permission should be sought from the WHO to provide the Institute with this information.