

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Appeal Hearing

Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the secondary prevention of osteoporotic fragility fractures in postmenopausal women

Decision of the Panel

Introduction

1. An Appeal Panel was convened on 15th September 2008 to consider an appeal against the Institute's Final Appraisal Determination, to the NHS, on the use of alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the secondary prevention of osteoporotic fragility fractures in postmenopausal women.
2. The Appeal Panel consisted of Professor Sir Michael Rawlins (chair of the Panel and chair of the Institute), Ms Jenny Griffiths (non-executive director of the Institute), Dr Peter Brock (industry representative), Ms Jean Gaffin (patient representative), and Professor Robin Ferner (NHS representative).
3. The Panel considered appeals submitted by Servier Laboratories Ltd.
4. In addition, the following individuals involved in the appraisal were present and available to answer questions from the Appeal Panel : Professor Andrew Stevens (chair of the Appraisal Committee), Dr Carole Longson (Director, Centre for Health Technology Evaluation), Professor Ken Stein (member of the Appraisal Committee), Dr Elisabeth George (Associate Director, Centre for Health Technology Evaluation) Dr Ruaraidh Hill (Technical Lead).

5. The Institute's legal advisor (Mr Stephen Hocking, Beachcroft LLP) was also present.
6. Under the Institute's appeal procedures members of the public are admitted to appeal hearings and several members of the public were present at this appeal.
7. There are three grounds on which an appeal can be lodged:
 - a. The Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute's Guide to the Technology Appraisal Process;
 - b. The Institute has prepared guidance that is perverse in light of the evidence submitted;
 - c. The Institute has exceeded its legal powers.
8. The chair of the Appeals Committee (Mr Mark Taylor), in preliminary correspondence, had confirmed that Servier Laboratories Ltd, the appellant, had potentially valid grounds of appeal as follows: Grounds 1, 2, and 3 (for ease of reference the numbering of appeal points in this letter is taken from Servier Laboratories initial letter of appeal).
9. The Final Appraisal Determination considered at this Appeal provided guidance on treatments designed to protect postmenopausal women who had suffered one osteoporotic fragility fracture from suffering further fractures. The medicines considered were the bisphosphonates alendronate, etidronate and risedronate; the selective oestrogen receptor modulator raloxifene; and the divalent strontium salt strontium ranelate.

Ground 1: The Institute has failed to act fairly and in accordance with its procedures

Servier Appeal Point 8. The Appraisal Committee has failed to adequately detail the economic analysis undertaken to examine the

implications of proton pump inhibitor use in patients taking bisphosphonates

10. Dr Neil Pumford, for Servier, argued that the Appraisal Committee had failed to give adequate details of the economic analyses of the effects of proton pump inhibitors in paragraph 4.2.29 of the Final Appraisal Determination. This went against the recommendations in paragraph 1.1.1 of the Guide to the Technology Appraisal Process.
11. Dr Elisabeth George, for the Appraisal Committee, directed the Appeal Panel to the description at page 19 of the report by Dr Stevenson entitled *Analyses of cost-effective BMD scanning and treatment strategies for generic alendronate, and the cost effectiveness of risedronate and strontium ranelate in those people who would be treated with generic alendronate* and to paragraph 4.2.29 of the Final Appraisal Determination. The modelling of the data with proton pump inhibitors was set out in the same degree of detail as the modelling of the data in the absence of proton pump inhibitors.
12. Dr Pumford confirmed that Servier had been provided with Dr Stevenson's report.
13. Mr Trefor Jones, for Servier, accepted that the estimates used in the model (and described at page 19 of Dr Stevenson's report) were reasonable and appropriate.
14. The Appeal Panel noted the judgement of the Court of appeal in *Eisai*, but also noted that case was under appeal to the House of Lords, and that the Court of Appeal had not ordered the release of the economic model in that case until the appeal to the House of Lords was concluded. It decided that the *Eisai* judgement did not require further release of analysis in this case at this time. The panel also noted that Servier Laboratories were challenging non-release of the economic model in this case in a judicial review application, and considered that the merits of any challenge on that basis would have to be resolved in the judicial review itself. The panel therefore concluded that the Appraisal Committee had described the economic analysis of the putative effect of proton pump inhibitors on fracture risk in sufficient detail for the consultees to provide intelligent comment on the analysis. There had been no unfairness.
15. The Appeal Panel therefore dismissed the appeal on this point.

Ground 2: The Final Appraisal Determination is perverse in the light of the evidence submitted

Servier Appeal Point 2. By failing to properly consider important scientific information demonstrating an association between proton pump inhibitors and fracture risk the Institute has failed to make

appropriate recommendations for this data in the Final Appraisal Determinations

16. Servier confirmed that they were content to discuss this issue in public, and that there were no confidentiality considerations in play.
17. Dr Pumford stated that there was strong evidence that proton pump inhibitors increased the risk of fracture in patients taking bisphosphonates such as alendronate. This evidence came from three published studies and a study utilizing the General Practice Research Database, which had been published in part, in abstract form.
18. Acid suppressant medication significantly reduced the benefits of bisphosphonates, and the Appraisal Consultation Document at paragraph 4.3.34 had advised prescribers that *“caution should be exercised when considering the co-prescription of acid-suppressive medication and bisphosphonates.”*
19. That advice had been altered, without good reason, in paragraph 4.3.38 of the Final Appraisal Determination, where the caution read *“Committee was not persuaded by this evidence”* and that *“caution should be exercised when considering the evidence about co-prescription of acid-suppressive medication and bisphosphonates”* (emphasis added by Servier).
20. Dr Pumford accepted that the first study on which Servier relied to demonstrate that there was a substantial danger from co-prescription was written by Vestergard et al [Calcif Tissue Int 2006;79:76–83], who concluded that: ‘Proton pump inhibitors appeared to be associated with a limited increase in fracture risk, in contrast to histamine H₂ antagonists, which seemed to be associated with a small decrease in fracture risk. In all cases, the changes in risk estimates were small and the clinical significance was limited.’
21. Dr Sarah Cockles, for Servier, stated that the best published study was that of Yang *et al* [JAMA 2006;296:2947-2953], which was the first study, and which identified an important risk. She agreed that the study by Yu, published in abstract, showed no significant increase in fracture risk with proton pump inhibitors, and that the results regarding histamine H₂-antagonists were contradictory.
22. Dr Cockles also accepted that the unpublished data from the analysis by de Vries et al showed an increased risk of fracture in all patients who took proton pump inhibitors, regardless of whether they took bisphosphonates. Indeed, only 2.6% of the cohort took proton pump inhibitors and bisphosphonates together.
23. Professor Tim Spector, retained by Servier, stated that more patients taking alendronate required proton pump inhibitors. While perhaps one patient in five took a proton pump inhibitor prior to prescription of alendronate, anecdotally,

that proportion might increase to one in three patients while they took alendronate.

24. Dr Pumford accepted that the level of concern had not been sufficient for Servier to contact the regulatory authorities, nor had any of the *Summaries of Product Characteristics* for bisphosphonates or proton pump inhibitors been amended to signal a potential interaction. The Food and Drug Administration was, however, investigating the possible interaction.
25. Professor Stevens, for the Appraisal Committee, stated that his Committee had considered the issue but had not been convinced that there was any clear or substantial evidence that proton pump inhibitors altered the fracture risk with alendronate. It might be that more patients who took alendronate rather than strontium ranelate required proton pump inhibitors but the effect of this, if any, on fracture risk was unclear. Consultees had, furthermore, pointed to evidence of important adverse effects from strontium ranelate. These included gastrointestinal adverse effects. Strontium ranelate was suspected to increase the risk of venous thromboembolism. The Appraisal Committee had decided not to introduce factors to allow for these added costs in the use of strontium ranelate, which had therefore been treated in a similar way to alendronate in this respect.
26. Dr George pointed out that, after the Appraisal Consultation Document was published, consultees advised the Committee that a further study had failed to find any change in fracture rate when proton pump inhibitors and risedronate were co-prescribed.
27. The Appeal Panel considered that the evidence that proton pump inhibitors or other acid-suppressant medication increased the fracture risk was weak. If a risk existed, it was likely to operate whether or not the patient was taking a bisphosphonate. Patients taking bisphosphonates were perhaps more likely to be taking proton pump inhibitors than patients taking strontium ranelate, but that had not been established. The Appraisal Committee had obviously considered the matter carefully and had taken into account the views of consultees. The Appeal Panel considered that the Appraisal Committee's conclusions about a putative association between acid suppressant medication and fracture risk were reasonable and not perverse.
28. The Appeal Panel therefore dismissed the appeal on this point.

Servier Appeal Point 5. The Appraisal Committee has been perverse in amending the T-score values for etidronate, risedronate and raloxifene without justification

29. Dr Pumford explained that paragraphs 1.2 and 1.3 of the Appraisal Consultation Document and the Final Appraisal Determination contained tables of recommendations which classified women by age and by the number of clinical risk factors into 18 groups, and presented the T-score for each of the groups below which treatment was cost-effective. For risedronate and etidronate, the values for 14 of the 18 groups had been altered between

the Appraisal Consultation Document and the Final Appraisal Determination, but for strontium ranelate, only one value had changed. This was unexplained, and to the benefit of risedronate and etidronate, but not strontium ranelate.

30. Dr Pumford also argued that strontium ranelate was clearly effective in the prevention of hip fractures, but this was not true of raloxifene. The efficacy of strontium ranelate had been accepted by the European Medicines Evaluation Agency (EMA). While it was true that the result came from a *post hoc* analysis, that was an analysis specified by EMA.
31. Dr Oana Bernard-Poenaru, for Servier, agreed that this *post hoc* analysis had been limited to elderly patients, and to patients with lower T-scores than had originally been stipulated. She also agreed that the *post hoc* analysis was one of a substantial number performed, although the only one regarding hip fractures. She accepted that there was scope for false-positive results from such analyses.
32. Professor Stevens described how calculations had been made of the effectiveness and cost of risedronate and etidronate that took into account the costs of identifying cases and of adverse effects, as described in the Appraisal Consultation Document. The Appraisal Committee had received comments on the Appraisal Consultation Document from the Guideline Development Group, to the effect that these costs would already have been incurred in treating those patients who switch from alendronate to risedronate or etidronate, and should not be added to the costings for these drugs. The T-score values had therefore been amended to take account of the lower calculated overall cost of treatment with risedronate or etidronate. This was explained in paragraph 4.3.17 of the Final Appraisal Determination.
33. Professor Stevens described how, by contrast, the additional costs of case-finding and of adverse effects had never been included in the calculations of the cost-effectiveness of strontium ranelate.
34. Dr George drew attention to paragraph 4.3.22 of the Final Appraisal Determination
35. Mr Jones accepted that the Company had failed to appreciate this.
36. The Appeal Panel considered that the Appraisal Committee had acted properly in considering the views of consultees regarding the Appraisal Consultation Document. It had been logical to reduce the costs associated with case-finding and adverse effects which explained the changes in the tables for risedronate and etidronate that were the focus of the appeal point. The end result in the FAD was that costs for risedronate and etidronate and for strontium ranelate were treated in the same way.
37. The Appeal Panel also accepted that the evidence that strontium ranelate was more efficacious than raloxifene was weak.

38. The Appeal Panel therefore dismissed the appeal on these points.

Ground 3 The Institute has exceeded its legal powers

Servier Appeal Point 11. The Appraisal Committee has exceeded its powers in taking actions that are not in accordance with the Human Rights Act and associated legislation

39. Servier alleged that the Institute had failed to comply with articles 2,3,8, and 14 ECHR, and in particular has breached art 14 read in conjunction with articles 2,3, or 8 by discriminating against patients on the sole basis of their age or disability.
40. Servier also alleged that the Institute had failed to comply with its own equality action plan which committed the Institute to complying fully with the general and specific duties contained in equalities and anti-discrimination legislation. In particular the plan states that recommendations should be made for a particular age group only where there is clear evidence of differences in clinical effectiveness that cannot be identified by any other means.
41. Mindful of its duties under s. 49A of the DDA, the panel asked Servier if they also relied on the DDA, and they confirmed that they did. They were given the opportunity to specify which sections of the DDA they considered to be in play after the close of the hearing. A paper was subsequently received and considered by the panel. Within that paper it was argued that the FAD discriminates between patients able to take alendronate and those unable to do so, and also between those able to take alendronate and risedronate/etidronate and those unable to do so. Servier asserted that it was necessary, to avoid unlawful discrimination, for a patient contraindicated alendronate to have access immediately to alternative treatment on the same criteria as would apply for access to alendronate. Failure to do so was contrary to s.49A DDA and s.21B(1) and 21D(1)(a) DDA.
42. During the appeal Professor Spector presented clinical vignettes illustrating the sorts of patients for whom treatment was not recommended.
43. For its part the appraisal committee said that it had discussed these issues very carefully, devoting most of one meeting to them. As a general observation, it commented that alendronate was both less expensive and more effective than the other drugs being appraised. Any use of any of the other drugs was, therefore, an adjustment being made in favour of minority groups, for example those who cannot take alendronate by reason of a disability. All of these alternative treatments represented a less cost-effective use of resources than alendronate. The committee had also specified in the FAD that support should be given to people with disabilities to enable as many of them as possible to take alendronate.
44. As regards age, it said that this was one of the strongest independent risk factors for an osteoporotic fracture. It would have been a charade not to

include age as a consideration. It was correct that age as used in the recommendation was treated as a threshold rather than a continuous variable, but no workable alternative presented itself. Further this approach was not unique to age, being adopted also for T scores.

45. As to Professor Spector's clinical vignettes, the appraisal committee did not feel that the issue was likely to be as common in practice as the clinical vignettes suggested.
46. The panel noted that, as regards the allegation of breaches of the Human Rights Act, these issues had been considered at length in its earlier appeal decision in this appraisal, published in December 2007. The panel will not repeat its view of the law set out in that letter here.
47. Applying that view of the law to the facts of this case, the panel remains of the view that access to these treatments is not within the ambit of any substantive ECHR right, and that therefore both the argument that those rights have been substantively breached and the argument that art 14 is breached fail. If that view were to be wrong, and in contrast to the position under the original guidance appealed against in 2007, the panel would have concluded that the various groups for whom treatment is not recommended (for instance, those in whom alendronate was contra-indicated and yet not meeting the criteria for treatment with etridronate or risendronate) do not constitute a group for the purposes of Art 14. For example, one such group would be women aged 65-69, with one risk factor, and a T score between -2.5 and -3.4. The panel does not accept that patients with T scores between any particular two values, and with age in a certain range, and with one risk factor, constitute a group protected by Art 14. Nor does it consider that it would be intellectually justifiable to focus on one of a range of factors determining whether treatment is recommended (for example age) and argue that that could constitute a group for Art 14 purposes since that would not reflect the true substance of the decision under challenge.
48. Further the panel would have concluded that any discrimination there may be is proportionate and in pursuit of a legitimate objective, namely the cost-effective use of NHS resources, and therefore justified.
49. As regards disability discrimination contrary to the DDA, the panel accepted that, consistent with its previous decision, there will be some patients who are unable to receive alendronate due to a disability, and that some of those patients would not be recommended for treatment with an alternative drug. However in the light of the House of Lords decision in *LB Lewisham v Malcolm* the Panel was not persuaded that this amounts to discrimination. The conduct in question is the patient not being recommended for treatment with an alternative to alendronate. The panel regards the reason for these patients not being recommended for treatment as being the decision that the treatments are not sufficiently cost-effective. That is not a reason relating to the patient's disability. Further, in the light of *Malcolm*, these patients fall to be compared with a patient who also cannot take alendronate but for a

reason unrelated to a disability. Those patients would be treated in exactly the same way as patients for whom the reason for not taking alendronate was a disability. Therefore there is no difference in treatment and no discrimination.

50. Furthermore, the panel would have held that any difference in treatment was justified, being proportionate, and in pursuit of a legitimate objective.
51. Finally under the DDA the panel considered the general duty under s.49A, but concluded that the committee had clearly been very mindful of the position of patients with disabilities, and indeed had made specific recommendations with such patients in mind. The appeal panel itself carefully considered the position of the relatively lower risk women who were unable to tolerate alendronate but were not recommended for treatment, and was satisfied that the recommendations were an appropriate balance between their needs and the need to secure cost effective use of NHS resources.
52. As regards the Institute's equality scheme, in so far as this expresses a commitment to comply with the Institute's legal obligations, it takes matters no further. In so far as there is a specific reference to the use of age as a criterion for recommendation for treatment, the panel observes that the scheme envisages that this is appropriate where there is clear evidence of differences in clinical effectiveness that cannot be identified by other means. The panel noted that age is itself a risk factor for fracture. The appellant urged that some other measure should have been used as a substitute for age, but in so far as that measure was merely a proxy for age-related risk, it would be a sham, and in so far as it was not a proxy for age related risk it would fail to capture what the committee considered to be an important indicator of fracture risk.
53. For all of these reasons the appeal panel dismissed the appeal on this point.

Conclusion

54. The appeal panel therefore rejects this appeal on all grounds.
55. There is no possibility of further appeal within the Institute against this decision of the Appeal Panel. However, the decision of the Appeal Panel may be challenged by an interested party through an application to the High Court for permission to apply for judicial review. Any such application must be made promptly and in any event within three months of this Decision or the issuing of the Guidance.