

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE
Health Technology Appraisal

Appeal Hearing

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

Decision of the Panel

Introduction

1. An Appeal Panel was convened on 22nd October 2007 to consider an appeal against the Institute's Final Appraisal Determination (FAD), to the NHS, on the use of alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary 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), Mr Jonathan Tross (non-executive director of the Institute), Dr Angus Sim (industry representative), Mr Lester Firkin (patient representative), and Professor Robin Ferner (NHS representative).
3. The Panel considered appeals submitted by:
 - i. The Alliance for Better Bone Health (Sanofi-Aventis and Procter & Gamble Pharmaceuticals UK Limited)
 - ii. The National Osteoporosis Society, for and on behalf of the National Osteoporosis Society, the Society for Endocrinology, the British Society for Rheumatology and the Bone Research Society
 - iii. 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 David Barnett and Dr

Michael Davies (members of the Appraisal Committee), Professor Peter Littlejohns (Executive Lead), and Dr Elizabeth George (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:
 - i. 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;
 - ii. The Institute has prepared guidance that is perverse in light of the evidence submitted;
 - iii. The Institute has exceeded its legal powers.
8. The chair of the Appeals Committee (Mr Mark Taylor), in preliminary correspondence, had confirmed that the appellants had potentially valid grounds of appeal as follows:
 - i. The Alliance for Better Bone Health (Sanofi-Aventis and Procter & Gamble Pharmaceuticals UK Limited): Grounds 1 and 2
 - ii. The National Osteoporosis Society: Grounds 1, 2, and 3
 - iii. Servier Laboratories Ltd: Grounds 1, 2, and 3
9. The Final Appraisal Determination considered at this Appeal provided guidance on treatments designed to protect postmenopausal women from osteoporotic fragility 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 published procedures

Alliance for Better Bone Health appeal point 1.1. The focus on initiation of pharmacotherapy is inconsistent with the original scope for the appraisal, and the change in scope introducing this new focus is both inconsistent with the appraisal procedure and unfair

10. Dr Jacqueline Bore, for the Alliance, stated that the scope for this Appraisal had been arbitrarily changed to focus on the initiation of treatment, and had therefore made no provision for the treatment of patients who were intolerant of alendronate, or in whom it was contraindicated. By contrast, the Institute's Technology Appraisal TA87, (of which the current Final Appraisal Document was an updated version, had considered this group of patients and made recommendations for their treatment. The appraisal process for the current Final Appraisal Document had begun in 2002 with a scoping exercise that had involved the Institute and the appellant. The scope had been revised in 2004. Two successive appraisal consultation documents had been produced according to these agreed scopes. The Appraisal Committee had then, and without prior consultation with the Alliance, produced a third Appraisal Consultation Document in February 2007 that considered only the initiation of therapy. This was unfair.
11. The original referral from ministers, and the subsequent scope, had referred to 'the clinical and cost effectiveness of selective oestrogen receptor modulators (SERMs), bisphosphonates, and parathyroid hormone (subject to licensing) for the prevention and treatment of osteoporosis and the prevention of osteoporotic fractures in post-menopausal women, and to provide guidance to the NHS in England and Wales.' It had been agreed with consultees that there should be two separate Final Appraisal Documents, one for primary prevention of fractures, and one for secondary prevention in those who had already sustained a fracture associated with osteoporosis.
12. Dr Longson accepted that the Appraisal Committee had refocused the scope to consider only initiation of therapy. The Committee had a difficult task to maintain adherence to the scope of the technological assessment and to share tasks suitably with the Guideline Development Group, whose purpose was to

13. Professor Peter Littlejohns stated that the Institute's view was that the NHS should take the advice contained in Clinical Guidelines issued by the Institute fully into account, although the Secretary of State's funding directive applied only to Technology Appraisals.
14. Dr Longson confirmed that the Institute had made no formal approach to the Department of Health.
15. Professor Andrew Stephens made it clear to the Appeal Panel that the Appraisal Committee considered alendronate cheaper and more effective than alternative treatments, and suitable for a substantial majority of patients.
16. Dr Longson explained that, in effect, the Appraisal Committee had not considered the question of those with disabilities – such as disorders of oesophageal motility – that prevented them from taking alendronate. She accepted that the Final Appraisal Document made reference to the companion Clinical Guideline, even though no date had been set for its publication. and the detailed content of those guidelines could not be known. She also accepted that the Appraisal Committee had not strengthened the references to

the Clinical Guidelines to indicate that they should carry the same weight as the Final Appraisal Document itself.

17. The Appeal Panel first considered whether it was correct to describe the scope of the appraisal as having been changed. The Panel considered that it was necessary to distinguish between a case where the Committee had considered the evidence relating to all or substantially all patients or uses of a technology within a scope, but had decided that that evidence did not allow any final recommendation to be made in some cases; and a case where the Committee had failed to consider at all certain patient groups or uses of a technology within a scope. The Appeal Panel considered that the former would not be a change of scope, whereas the latter would be. The Appeal Panel considered that in this case the scope had in effect been altered, since the Committee had stated that the reason for not taking a decision, for example, regarding patients in whom alendronate was contraindicated, was the desire to leave that decision to the Guideline Development Group, and not because of any defect in the evidence base.

18. The Appeal Panel noted there was no express provision within the Institute's procedures for an appraisal to be limited within its scope as in this case. The Panel considered that the Institute's procedures required an appraisal to be conducted across the full breadth of its scope, unless there is a clear reason, relating to the evidence, why this could not be done.

19. The Appeal Panel also considered whether the consultation inherent in the Appraisal Consultation Document published after this change was sufficient to rescue any unfairness that this change may have caused. As a general rule, consultation by way of an Appraisal Consultation Document would be sufficient to ensure fairness. However, the panel concluded that in this specific instance it was not. A fundamental change, introduced late in the appraisal process, had been made that represented a departure from its consistent past practice and was apparently in breach of the Institute's procedures. Fairness would have required a separate consultation. By publishing the Appraisal Consultation Document, and having in mind the stated reason for the change, it appeared that the Committee's mind on this issue was already made up. Indeed, the Committee did not seek to argue otherwise.

20. The Appeal Panel therefore upheld the appeal on this ground.

21. Although not raised by the appellants there is a further matter on which the Committee's actions in this appraisal must not be upheld. The Appeal Panel also decided that there were groups of patients with disabilities, as legally defined, such as those with Parkinson's disease, in whom alendronate would generally be contra-indicated. Failing to consider providing advice on the treatment of these disabled patients meant that they were disadvantaged. The Appeal Panel considers that this would amount to unlawful discrimination on the grounds of disability. To avoid this discrimination the Appraisal Committee must consider providing advice on the value of other treatments in those patients who could not take alendronate. If it feels that it is unable to provide advice for those patients, it should give reasons.

22. The Appeal Panel considered it to be helpful to make a general observation on the relationship between an appraisal and the development of a clinical guideline. It noted that the end product of an appraisal may, as a result of the Secretary of State's directions, have more or less direct consequences for funding. It also noted that participants in an appraisal had certain rights and safeguards, most notably the right of appeal, that do not apply to the development of a clinical guideline. As a general rule, therefore, it did not consider that it would be appropriate for any part of a technology appraisal to defer to or be delegated to the production of a clinical guideline. This might deny patients the benefit of the funding direction, and consultees the benefit of an appeal. The Appeal Panel accepted that a technology appraisal should not set out a pathway of care, but the Institute should be aware that any appraisal process that does not, at a minimum, examine the use of the technology being appraised in all significant patient groups within scope, and make recommendations where the evidence permits this, is very likely to be rejected on any appeal. The Appeal Panel recommended that guideline development groups should be made aware of this position.

Alliance for Better Bone Health appeal point 1.2. The comparisons made between different bisphosphonates are inconsistent with the appraisal scope, unfair and not sufficiently transparent

23. Dr Bore explained to the Appeal Panel that the Final Appraisal Document relied on an analysis in which data from alendronate and risedronate were pooled together. It appeared that because alendronate was 'so very cheap', the Appraisal Committee had ignored the possibility that other treatments might still be cost-effective. Costs for dual X-ray absorption (DEXA) scans were apparently included for all patients. The methods used to examine cost-effectiveness were opaque, because the Alliance had not been provided with a read-only copy of the mathematical model used. This was unfair.
24. Professor Stephens explained that combining the results of clinical trials, for drugs within the same therapeutic class, was a common practice in meta-analyses and provided the most reliable estimates of effect size. In this instance, combining the results of clinical trials of alendronate and risedronate favoured the latter because the effect sizes of the former were somewhat greater.
25. Professor Stephens also stated that, in estimating cost-effectiveness, costs that were inevitable in the deployment of a technology were included. For example, the cost of determining oestrogen receptor status in patients with breast cancer was included in the assessment of the drug trastuzumab (Herceptin®). The Appraisal Committee had viewed the cost of DEXA scanning in this way, but had taken precautions to count it only once for each relevant patient.
26. Dr Longson regretted that the Appraisal Committee had been unable to provide a copy of the mathematical model. This used data from a World Health Organisation (WHO) study. The Committee had been bound by an academic confidentiality agreement to keep the WHO data secret until they were published, and had been assured by the authors that they would be published in 2005.

27. Professor Stephens said that the WHO data included risk factors for fracture that were independent of bone mineral density. The Appraisal Committee had taken a cautious approach to the data, and included them with weights of 0.5.
28. The Appeal Panel decided that, in combining efficacy data for alendronate and risedronate, the Appraisal Committee had not acted unfairly. The Appraisal Committee had to make a choice between a more precise estimate for the efficacy of two similar drugs, and a less precise estimate for each separately. There was no evidence that risedronate had been disadvantaged.
29. The Appraisal Committee had appropriately considered the cost of DEXA scanning, and had acted in conformity with other appraisals. Inclusion of this cost in a relevant way was not unfair.
30. The processes of the Institute do not require the Appraisal Committee to release the model if it is confidential for academic or commercial reasons. There are strong public policy reasons for enabling the Institute to obtain, and use, all relevant data even if some of the data are supplied under obligations of confidentiality that mean that the Institute cannot be as transparent as it might otherwise wish. Any party might claim the benefit of confidentiality and, indeed, a manufacturer had done so in this appeal. The Appeal Panel considered that withholding a read-only version of the mathematical model used to model cost-effectiveness had not been unfair.
31. The Appeal Panel therefore rejected the appeal on this point.
32. It was evident that the Appraisal Committee was frustrated by the failure of the World Health Organisation (WHO) to publish its model; and the Appeal Panel was clear that, but for the WHO's wish for the model to remain academic-in-confidence, the Appraisal Committee would have offered to release it to the consultees in read-only form. The Appeal Panel considered that the WHO's failure to publish, for some years, data of considerable public importance was regrettable; but that, in all the circumstances, the Institute had not acted unreasonably.

National Osteoporosis Society appeal point 1.1. The Institute changed the scope for these appraisals part way through the process and without consultation

33. Mrs Claire Severgnini, for the National Osteoporosis Society, explained that the Society had not been consulted on the change of scope. If it had been consulted, it would have objected strongly to the changes, which excluded consideration of those who were intolerant of, or unresponsive to, first-line treatment. Guidelines developed by the Guideline Development Group were very important, but they were not mandatory on NHS funding bodies.
34. The Appeal Panel had accepted (see paragraph 19 and 20) that the late change in the scope without prior consultation was unfair as discussed above.
35. The Panel therefore upheld the appeal on this point.

National Osteoporosis Society appeal point 1.4. The Appraisal Committee has been inconsistent in its use of inputs and assumptions in the economic model, making changes despite there being no new evidence

36. Dr Peter Selby, for the National Osteoporosis Society, claimed that the fall in the cost of alendronate should have had the effect of increasing the size of the population in whom treatment was cost-effective; but that this had not happened. This was in part because the Appraisal Committee had chosen to change the values of costs associated with osteoporotic fractures. The cost of caring for a patient with hip fracture had been put at £6750, while earlier it had been taken as £8538. The harm from vertebral fractures had been reduced, so that the utility had been altered from 62.6% of normal to 79.2%. A much larger value had been used for the proportion of patients suffering adverse reactions to the drugs.
37. Professor Stephens explained that the costs of hip fractures were taken from the standard NHS dataset; in fact, there were 16 different sorts of fracture considered in the model, but in only one case had the cost fallen, and that was the figure that the National Osteoporosis Society had chosen to describe. The figures for harm from vertebral fractures had been altered because the data referred only to women admitted to hospital, who represented a small minority of patients with vertebral fractures. There were good reasons for

altering the estimates of adverse reactions to the drugs, but in practical terms, the effects of allowing for adverse drug reactions on the cost-effectiveness model was small.

38. The Appeal Panel considered that the changes to the inputs to the model had not been unfair.

39. The Appeal Panel therefore rejected the appeal on this point.

National Osteoporosis Society appeal point 1.5. The approach followed in relation to the appraisals of osteoporosis treatments is not consistent with other appraisals and has significantly reduced cost-effectiveness estimates

40. Professor Roger Francis, for the National Osteoporosis Society, argued that the inclusion of costs for case-finding was wrong. The cost of cholesterol testing was not included in economic evaluations of statins, by contrast. For some patients, such as those with rheumatoid arthritis, there were no costs associated with case-finding. The cost-effectiveness had been computed over ten years, whereas in other appraisals it had been computed over the lifetime of the patient. This inconsistent approach was unfair.

41. Professor Stephens reiterated that where the test was a necessary prelude to treatment, then its cost was included. He also pointed out that benefits in mortality were calculated over the patient's lifetime for this, and for previous, appraisals. Benefits in respect of morbidity had, as in many other appraisals, been calculated over a 10 year time-frame. The approach taken by the Appraisal Committee, in this appraisal, was therefore consistent.

42. The Appeal Panel concluded that the Appraisal Committee's approach to the costs of case finding taken were reasonable, as was its approach to the inclusion of mortality and morbidity benefits; and that these were consistent with other appraisals.

43. The Appeal Panel therefore dismissed the appeal on this point.

44. However, the Appeal Panel recommends that the Appraisal Committee makes the approach to mortality benefits clearer in the FAD.

National Osteoporosis Society appeal point 1.6. No explanation has been provided for the use of clinical risk factors used to identify patients at the highest risk of fractures

45. Dr Selby claimed that the risk factors for osteoporosis were difficult to follow, in the Guidance, and that the Appraisal Committee's approach appeared to have changed since the publication of the related technology appraisal, TA87.
46. Professor Stephens explained that risk factors for osteoporotic fractures were categorised into those that were dependent, and those that were (at least partly) independent, of bone mineral density. The latter (FAD 2.11) included parental history of hip fracture, alcohol intake of 4 or more units daily, and severe long-term rheumatoid arthritis. Guidance on the clinical and cost effective use of products for the primary prevention of osteoporosis (FAD 1.3 and 1.4) were intended to reflect this.
47. The Appeal Panel considered that this approach was evidence-based and reasonable; and could not be regarded as unfair.
48. The Appeal Panel therefore dismissed the appeal on this point.

National Osteoporosis Society appeal point 1.7. There is no indication that the committee considered the factors set out in sections 6.2.6.10 and 6.2.6.11 of the Methods Guide. The decision to present ICERs only below £20,000 for primary prevention means it is impossible to see the effects of sensitivity analyses or the reasons for the rejection of treatment. £20,000 has been treated as a rigid threshold.

49. Professor Stephens (with Professor Barnett concurring) explained that the Appraisal Committee had, indeed, considered the special circumstances outlined in sections 6.2.6.10 and 6.2.6.11 of the Methods Guide but did not consider, in these circumstances, that any were applicable to this appraisal. By contrast, the committee considered that some special circumstances applied in the secondary prevention of osteoporotic fractures and, hence, were prepared to adopt a higher cost per QALY for that appraisal. Professor Stephens, in response to questions from the Panel, explained "willingness to pay" in FAD 4.2.3 represented a "societal" value rather than an individual one.

50. The Appeal Panel accepted that the Appraisal Committee had given full consideration to the issues in sections 6.2.6.10 and 6.2.6.11 of the Methods Guide but had concluded that none could be applied to the primary prevention of osteoporosis. The panel concluded that the committee had not been unfair.

51. The Appeal Panel dismissed the appeal on this point but considered that the FAD would be improved by the inclusion of a short statement explaining the committee's reasoning.

National Osteoporosis Society appeal point 1.9. The recommendations contained in the Final Appraisal Document will limit innovation in the field of osteoporosis

52. Mrs Severgnini stated that the mandatory use of only one drug would discourage innovation in the field of osteoporosis.

53. Professor Stevens assured the Appeal Panel that the Appraisal Committee always took innovation into account, and had considered the extent to which the technologies in this appraisal filled a therapeutic vacuum or were extraordinarily innovative.

54. The Appeal Panel was satisfied that the Appraisal Committee had considered whether the recommendations in the Final Appraisal Document would inhibit innovation. The Appraisal Committee had not been unfair.

55. The Appeal Panel therefore dismissed the appeal on this point.

Servier appeal point 1.1. The Appraisal Committee has failed to take account of an important piece of scientific evidence; the Appraisal Committee has demonstrated internally inconsistent decision making with the generalisation of relative risk data generated in low risk patients and extrapolated to all patients under consideration; the Appraisal Committee has demonstrated inconsistent decision making in standards applied both within this appraisal and compared to other appraisals in their application of the hierarchy of evidence

56. Dr Guy Yeoman, for Servier, contended that etidronate had been regarded favourably by the Appraisal Committee, on the basis of observational data, while evidence from a randomised, controlled trial of strontium ranelate that showed a statistically significant reduction in hip fractures had been disregarded.
57. Professor Stevens explained that the reduction in hip fracture rate described with strontium ranelate was only found in a *post hoc* analysis of a group of high-risk patients that had not been pre-specified. The Appraisal Committee had allowed for this weak evidence by setting the hip fracture rate with strontium ranelate to 0.85. The observational studies had failed to show a significant beneficial effect on hip fracture rate with etidronate, and the value for etidronate had been set to 1.0.
58. Dr Patricia Chatelain-Belissa, for Servier, explained that the *post hoc* analysis had been conducted at the request of the European Medicines Evaluation Agency (EMA). The Agency had altered the rules under which a licence would be granted to medicines used in the treatment of osteoporosis, and the change had come about during the course of the licensing studies for strontium ranelate. The studies were not designed to have the statistical power to find a reduction in the rate of hip fracture. The *post hoc* analysis was conducted for a high risk subgroup and demonstrated the proposed reduction in hip fracture risk to the extent necessary for EMA to grant a marketing authorization for that indication.
59. The Appeal Panel understood the difficulties facing Servier as a result of the change in the standards expected by EMA. The Panel also accepted that the Appraisal Committee had taken into account the evidence and evaluated it appropriately. It had not been unfair.
60. The Appeal Panel therefore dismissed the appeal on this point.

Servier appeal point 1.2 The Committee has changed the scope of the appraisal without direction from the DoH and without consultation

61. The scope had originally considered both clinical and cost-effectiveness, and included the possibility of recommending treatments for patients who were

intolerant of, or unsuitable for, treatment with first-line therapies. The scope had been changed at a very late stage. The change in scope meant that recommendations on second-line treatments were relegated to the clinical document. This would not carry the mandatory Funding Direction, which was only relevant to Technology Appraisals. Servier were not aware that they had been invited to comment on the new scope.

62. The Appeal Panel had already considered the change in scope, and found that it had been unfair for the reasons given above (paragraphs 18-20).

63. The Appeal Panel therefore upheld the appeal on this point.

Servier appeal point 1.4. The Appraisal Committee has failed to address new evidence

64. Dr Yeoman said that the Appraisal Committee had failed to take into account information submitted in May 2007 that, in the view of the Company, demonstrated an increased risk of fracture in patients taking proton pump inhibitors. Proton pump inhibitors were widely used to alleviate the adverse effects of bisphosphonates on the upper gastro-intestinal tract. By recommending that treatment only be initiated with a bisphosphonate, the Appraisal Committee was putting patients who required a proton pump inhibitor at increased risk. This contravened the principle of non-maleficence as laid down in the Institute's Social Value Judgements document.

65. Dr Longson explained that the Final Appraisal Determination was agreed at a meeting in April 2007.

66. The Appeal Panel observed that the Appraisal Committee was only obliged to take new evidence into account if the evidence was compelling, and that the information that led to Servier's appeal was not in this category. It had been submitted to the Institute after the final form of the Final Appraisal Document had been agreed. The Appraisal Committee could not have acted unfairly in failing to consider evidence submitted after it had made its Final Appraisal Document.

67. The Appeal Panel therefore dismissed the appeal on this point.

Servier appeal point 1.5. The Appraisal Committee has failed to provide the economic model on which the appraisal was based

68. Mr Trefor Jones, for Servier, described how the Company had been provided with a spreadsheet that showed only the results from the model. The macros used to calculate the results had been blacked out. This meant that many assumptions made in the model were unknown to the Company. Where assumptions were clear, the Company had sometimes noted the absence of adequate sensitivity analyses. In particular, the model assumed five years of treatment, and an effect that lasted for five years after the end of treatment, but there was no evidence for this duration of effect, and no sensitivity analysis to examine different durations.
69. Dr Longson accepted that there had been some difficulties in providing information on the model, as described in her responses to other appellants. These difficulties were not unique to the osteoporosis appraisal. They had not prevented Servier from making detailed and very clear comments on aspects of the model in response to the Appraisal Consultation Document.
70. Professor Stevens accepted that the duration of effect after treatment was not known, but argued that the Appraisal Committee had strong reasons for believing the assumed duration to be favourable to the treatments.
71. The Appeal Panel had already decided (above) that withholding a read-only version of the mathematical model used to determine cost-effectiveness had not been unfair (see paragraphs 30 and 31). The Appeal Panel also accepted that the Appraisal Committee had considered fairly whether appropriate sensitivity analyses had been conducted; and that the Committee's acceptance of the different time-frames for extrapolating mortality and morbidity were commensurate with practice in other appraisals (see above).
72. The Appeal Panel therefore dismissed the appeal on this point.

Servier appeal point 1.6. The Appraisal Committee has failed to act in accordance with the published procedure on encouraging innovation

73. Dr Yeoman reminded the Appeal Panel that the Social Value Judgment document provided by the Institute encouraged innovation. Strontium ranelate provided, in Servier's view, substantial health gains compared with other treatments to prevent fractures in patients with osteoporosis.
74. Professor Stevens stated that there were several effective treatments to prevent fractures in patients with osteoporosis, and strontium ranelate was not so innovative as to require special consideration.
75. Dr Alun Cooper, for Servier, stated that 40% of the population suffered from dyspepsia, and dyspepsia accounted for 5% of visits to General Practitioners. In osteoporotic patients who suffered from dyspepsia and required treatment to prevent fractures, the practitioner had difficulty in deciding what treatment was best.
76. The Appeal Panel considered that the Appraisal Committee had judged strontium ranelate by the same criteria as other treatments, taking innovation into account, and had not been unfair.
77. The Appeal Panel therefore dismissed the appeal on this ground.

Appeal Ground 2: The Institute has prepared guidance which is perverse in the light of the evidence submitted

Alliance for Better Bone Health appeal point 2.1. The recommendations are perverse because they do not take account of identifiable patient groups who cannot or should not receive alendronate as first line therapy

78. Dr Bore explained that the current Final Appraisal Document failed to make provision for women who were unable to take, or who should not take, once-weekly alendronate. The contra-indications to the use of alendronate differed from those for the other drugs. There were also circumstances, for example, in a care environment, where once-daily preparations were prescribed in preference to once-weekly preparations. The Final Appraisal Document did not provide for women in such circumstances.

79. Professor Stevens stated that the Guideline Development Group would consider the treatment of women who were unable to take once-weekly alendronate.
80. The Appeal Panel considered that there were some women who were unable to take, or who should not take, once-weekly alendronate. It was reasonable to expect the Final Appraisal Document to provide advice on how best to treat them although, as the Committee had not in fact considered these women at all, it was not strictly possible to say whether or not the Committee had acted perversely. It had instead failed to act at all. The Appeal Panel accepted that the advice might be complex. It might be helpful for the advice to be tabulated in the Final Appraisal Document. The Final Appraisal Document as presently written did not seek to provide this advice at all.
81. The Appeal Panel therefore did not determine the appeal on this point, but repeated that the underlying complaint was a valid appeal point for the reasons given under ground one above.

Alliance for Better Bone Health appeal point 2.2. The recommendations for bisphosphonate treatment are perverse because they are internally inconsistent, inconsistent with other technology appraisals and fail to recognise the clinical value of different dosage forms

82. Dr Bore advanced the Alliance's view that the Appraisal Committee was perverse to consider the efficacy of alendronate and risedronate together, but their costs separately. Furthermore, it was perverse to include the costs of DEXA scanning in the calculation of the costs of a second-line agent, when those costs had already been accounted for in providing the first-line agent. She also described circumstances, for example, in a care environment, where once-daily preparations were prescribed in preference to once-weekly preparations. The cost of once-daily alendronate was higher than the cost of once-weekly alendronate. The Final Appraisal Document did not provide for women in such circumstances.
83. Professor Stevens explained that the Appraisal Committee had considered carefully whether to pool efficacy data on alendronate and risedronate, and decided that this would give a better estimate of the effects of

bisphosphonates than separate analyses. In fact, alendronate appeared rather more effective than risedronate, so the analysis made risedronate appear more favourable than it might be in reality. The costs of the two drugs were very different, and this had been taken into account. The Appraisal Committee had not included the costs of DEXA scanning in computations of the cost of second line agents. Evidence before the Appraisal Committee demonstrated that a once-weekly treatment regimen improved adherence to treatment.

84. The Appeal Panel accepted that the Appraisal Committee had acted reasonably in using a pooled analysis to determine the efficacy of alendronate and risedronate together to give a more precise overall estimate of their effect. The Appraisal Committee had also been reasonable in the way it had included the cost of DEXA scanning. The once-weekly regimen had advantages, and might reasonably be recommended.

85. The Appeal Panel therefore rejected the appeal on this point.

Alliance for Better Bone Health appeal point 2.3. The focus on bone mineral density is perverse because it is inconsistent with the remit to advise on “the prevention and treatment of osteoporotic fractures” which requires a consideration of effects that cannot be explained by BMD increases alone.

86. Professor Stephens explained that the Appraisal Committee did not focus, exclusively, on increases in bone mineral density . Indeed, in FAD 1.3, 1.4 and 2.11, it is specifically stated that there are both dependent and independent risk factors associated with osteoporotic fragility fractures (see Paragraph 46).

87. The Appeal Panel concluded it was clear that the appraisal committee had incorporated dependent and independent risk factors for osteoporotic fragility fractures. The committee had not, therefore, been perverse in drawing its conclusions.

88. The Appeal Panel therefore dismissed the appeal on this point.

National Osteoporosis Society appeal point 1.2. The Institute has inappropriately based treatment decisions on age contrary to the NICE Social Value Judgements. In

particular, the FAD (4.1.2) assumed that the reduction in the relative risk remains constant at all ages

89. The Society claimed that the failure to base guidance on overall fracture risk, rather than simply by reference to age, is inconsistent with the principles laid out in Social Values Judgement.
90. The Appeal Panel pointed out that the assumption, in FAD 4.1.2, that the reduction in relative risk of osteoporotic fracture was independent of age did not infer that the absolute risk was similarly independent of age. Indeed, FAD 2.11 recognised that age was a risk factor for osteoporosis. The panel therefore considered that the use of age, in this appraisal, was fully compatible with the provisions of Social Value Judgements and that the Appraisal Committee had not been perverse.
91. The Appeal Panel therefore dismissed the appeal on this point.

National Osteoporosis Society appeal point 1.8. No explanation has been provided for the Appraisal Committee's apparent decision to set different cost-effectiveness thresholds for primary and secondary prevention

92. Professor Francis stated that women with hip fractures look very similar to those who are at risk of hip fractures but have not had one. It was therefore perverse to examine cost-effectiveness for one up to £30 000 per quality-adjusted life year (QALY), but the other only up to £20 000 per QALY.
93. Professor Stevens stated that the number of women whom it was necessary to treat for one to benefit in the group with hip fractures was much lower than in the group without hip fractures. Spending a great deal of money on treatment for primary prevention of osteoporotic fractures would deny the NHS the opportunity of treating other conditions. He emphasised that this was an important matter for the Appraisal Committee to consider. Furthermore he argued that in primary prevention the Committee were considering treating "well" patients, and that it was appropriate to exercise greater caution in that case.
94. The Appeal Panel accepted that the Appraisal Committee was only obliged to consider expensive treatments in specified circumstances, and if it decided to

recommend such treatments had to give clear reasons for doing so as exceptions to the general rule. It was not necessary to explain not making an exception. Its approach to primary and secondary prevention was reasonable.

95. The Appeal Panel therefore rejected the appeal on this point.

96. However, 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.

National Osteoporosis Society appeal point 2.1. The estimated incidence of side effects with bisphosphonates (multiplied by ten times) has been applied to all of the other treatments appraised which is perverse given that each of the other treatment classes have different modes of action, different side effect profiles and their own evidence base

97. Dr Selby stated that the adverse effects of bisphosphonates were not particularly severe. They were usually transient, and related to the administration of the drug. However, the Appraisal Committee had accepted an estimate of the harm from adverse effects that multiplied their importance by a factor of ten. This estimate had also been applied to the non-bisphosphonate drugs raloxifene and strontium ranelate.

98. Professor Stevens explained that the estimate of harm referred to one month of treatment, and the estimate had been multiplied by ten to allow for continued treatment. In any event, he agreed with Dr Selby that the adverse effects were not, generally, of great significance and did not substantially influence the calculations of cost-effectiveness.

99. Dr George stated that, in considering the cost per QALY for secondary prevention with alendronate, this was £18 550 if adverse effects were included in the model, and £17 903 if they were excluded. There was a typographical error at paragraph 4.2.21 of the Final Appraisal Document.

100. With regard to raloxifene and strontium ranelate, Professor Stevens clarified that no multiplier had been used, and so the contribution of adverse effects to the cost- effectiveness calculations was very small.

101. The Appeal Panel accepted that the Appraisal Committee's approach to adverse effects had been reasonable.

102. The Appeal Panel therefore dismissed the appeal on this point.

Servier appeal point 2.1. The Appraisal Committee has failed to take account of an important piece of scientific evidence

103. The Company provided evidence of an effect of proton pump inhibitors on fracture risk. This evidence included a scientific paper by Yang and colleagues [*Journal of the American Medical Association* 2006; **296**: 2947]. Further evidence relating to the same effect was provided to the Appeal Panel *in camera*, as was allowed under the Institute's rules. This evidence had been supplied to the Institute in May 2007.

104. Dr Longson reminded the Appeal Panel that the Final Appraisal Document had been agreed at a meeting in April 2007.

105. The Appeal Panel considered that the Appraisal Committee had taken into account the evidence presented to it prior to the meeting at which the Final Appraisal Document was agreed. Evidence submitted after that meeting (see paragraph 66) could not have been taken into account.

106. The Appeal Panel dismissed the appeal on this point.

Servier appeal point 2.2. The Committee has made recommendations that will result in increased fractures and increased expenditure

107. The Appeal Panel was told that failure to take the information on proton pump inhibitors into account would result in women being placed at increased risk of fracture.

108. The Appeal Panel had already determined that the Appraisal Committee had acted reasonably with regard to the data on proton pump inhibitors and a possible increase in fracture risk. The data were not so compelling that they required the normal processes of the Institute to be set aside.

109. The Appeal Panel therefore dismissed the appeal on this point.

Servier appeal point 2.3. The Appraisal Committee has demonstrated internally inconsistent decision making with the generalisation of relative risk data generated in low risk patients and extrapolated to all patients under consideration

110. Dr Yeoman argued that the Appraisal Committee had been unreasonable in accepting a subgroup analysis of high-risk patients from the alendronate Fracture Intervention Trial, but rejecting a similar analysis from the TROPOS study of strontium ranelate, even though that analysis had been accepted by the EMEA.

111. Professor Stevens assured the Appeal Panel that the Appraisal Committee had in fact used the information that was available.

112. The Appeal Panel had already determined that the Appraisal Committee had taken the results from the *post hoc* analysis into account. Its approach was reasonable.

113. The Appeal Panel therefore dismissed the appeal on this point.

Servier appeal point 3.1. The Appraisal Committee has amended the scope of the appraisal without direction from the Department of Health and without consultation with stakeholders

114. The Appeal Panel found (above) that the scope in this appraisal had been varied by the Institute without consultation and that this was unfair and not in accordance with , past practice.). The Appeal Panel does not feel it is necessary to rule separately on whether a specific direction from the Secretary of State / Welsh Assembly Government opposed to consultation) would have been needed before a valid variation could have been made.

115. Had it been argued, the Appeal Panel would have been minded to rule that the limitation in recommendations to initiation with one treatment only, with all other recommendations to be dealt with in a forthcoming clinical guideline, prepared by a different body and whose content was unclear at the time of the appraisal, was an unlawful delegation of a discretion, and unlawful for that reason.

116. The Appeal Panel makes no finding on this point.

Servier appeal point 3.2. The Appraisal Committee has exceeded its powers in taking actions that are not in accordance with the Human Rights Act (an essentially identical argument was advanced by the National Osteoporosis Society)

117. Servier argued that the treatment in question was within the ambit of art 8 of the ECHR (right to respect for private and family life), and contrary to art 14 (prohibition on discrimination) on two grounds, first, in excluding patients who are contraindicated for alendronate, and second, because the recommendations distinguish between women on the grounds of age.

118. The Appeal Panel considered first whether these treatments were within the ambit of Art 8. In doing so it had the benefit of papers submitted after the appeal hearing (at the Panel's request) on behalf of Servier and the NOS. Those papers also considered other articles of the ECHR. Although not strictly raised as appeal grounds it is helpful to consider them in turn.

119. Art 2: It was argued on behalf of Servier that these treatments are within Art 2 (the "right to life"). Art 2 is substantially a negative right: outlawing the taking of life. It does impose certain positive obligations, notably the obligation to investigate death and to take action to discourage the taking of life. Servier argued that Art 2 may encompass more substantive positive obligations to fund medical treatments that save life (Servier argued that the obligation was that a state "should not without justification refuse to fund medicines for a specific part of the patient population.")

120. There are difficulties with this argument. The cases cited do not directly support it (*Pretty* considered art 2 in the context of an alleged right to die,

rather than live, and the passage cited by Servier refers only to the well known positive obligations to investigate deaths. *Scialacqua* merely hypothesised an obligation to fund “treatments that are essential to save lives” without deciding that such an obligation existed. And in any event these drugs could not be described as “essential to save lives.”)

121. In the appeal panel’s view, Art 2 may require the state to make available a health service in some form, and (read with art 14) may require non-discriminatory access to whatever facilities which the state has decided to provide (see *NHS Trust A v M*, *Nitecki*.) The panel is not aware of any authority which suggests that global decisions on allocation of resources within a health service would fall within the ambit of Art 2, and would find such a position surprising. The panel considers that the Institute’s role is, for this purpose only, analogous to the position in *Scialacqua* where the court ruled that Art 2 “cannot be interpreted as requiring states to provide financial covering for medicines which are not listed as officially recognised medicines.” Here the issue is not official recognition, but a judgement on acceptable cost effectiveness, but the principle must be the same. Once a decision has been taken to make a treatment available in certain circumstances, Art 2 may apply to any failure to provide it in those circumstances. But Art 2 does not seem to apply to the decision as to whether the treatment should be available in the first place.

122. Art 3: Essentially the same arguments are advanced under Art 3, although with the added force that as Art 3 outlaws inhuman or degrading treatment, the objection that these drugs are not life saving falls away. *Pretty* is cited, with the suggestion that denial of pain killing drugs might have violated art 3 in her case.

123. The same objection applies to the argument under Art 2. The cases support the argument that if a drug was generally available, deliberately withholding it begs the question of whether the drug is to be generally available, which is the very decision to be made in this case. (Strictly, it is whether the drug is to be more or less generally available, since NICE neither licenses nor bans drugs). It would be surprising if a decision of a health service to focus its resources on securing the most cost effective treatment for its population engaged Art 3 rights for those who hoped to enjoy less cost effective

treatment, and there appears to be no authority that would suggest that Art 3 is engaged in this way.

124. Art 8: Servier cite *Passannante*, a case in which it was held that delay in providing medical treatment may engage art 8. Again, though, the argument assumes that the treatment was in principle generally available (and indeed that there was “an obligation” to provide it). Servier assert that the treatment in this case is available, in the sense that the Department for Health must be assumed to be willing to fund it. No doubt that is correct, in the sense that the treatment has not been listed as unavailable within the NHS, but the Department’s intention seems to be clearly spelt out in the Secretary of State’s funding direction, namely that treatments which are recommended by the Institute should be funded. Again, it begs the question to apply Art 8 to a decision as to whether, and if so when, a treatment should be made generally available. Furthermore, it is not clear that within the UK health service, which is funded from general taxation and not individual subscription, there can be said to be “an obligation” to provide treatment.

125. Servier also argue that Art 8 protects the right of a patient to consent to (or more usually refuse consent to) medical treatment. That is correct, but it is a non sequitur to argue that therefore all possible treatments must be available so that a patient may consent to them.

126. The Panel also considered the *Pentiacova* case, cited by the NOS, and concluded that this case supports the conclusion that, whilst some instances of medical treatment may be within the ambit of Art 8, (although strictly the court merely assumed this for the purposes of an admissibility hearing) this is only likely to be the case where the allegation is denial of access to a standard of treatment made generally available, and it is not likely that Art 8 is engaged where the issue is a general judgement on acceptable cost effectiveness (In ruling the complaint manifestly ill founded and inadmissible, the Court commented that “the applicants had access to the standard of healthcare offered to the general public...”) It was also notable that in *Pentiacova* the court referred to complaints about “insufficient funding of [the applicants] treatment” which suggests that the issue was affordability, rather than cost effectiveness. Affordability is outside the Institute’s remit.

127. The NOS drew attention to *Tysiack*, a case concerning the denial of access to abortion. Clearly the facts of that case are rather different to this appraisal, but the panel notes that the court affirmed that “the convention does not guarantee as such a right to any specific level of medical care.”
128. The panel also considered *Sentges*, a case in which it was held that Art 8 was only engaged where there was a "direct and immediate" link between the measure sought (in that case the provision of a robotic arm to assist a severely disabled person) and the applicant's private life. In that case the court held there was no such link. On its face, the provision of the robotic arm would seem to have much more impact on the applicant's enjoyment of private life than the provision of the drugs in this case, in that it would certainly have enabled him to carry out a wider range of day to day tasks for himself, and so enjoy more autonomy and self determination, which are concepts that sit within Art 8. And yet the court held Art 8 was not engaged. Once again the court observed that the facilities offered to the applicant met the standard of health care generally made available
129. Finally, on the facts of this case, the Panel was not persuaded that the effects of these treatments, although no doubt desired by patients, were sufficiently life-changing to engage any of articles 2, 3, or 8.
130. For all of these reasons, the Appeal Panel does not agree that any substantive rights under the ECHR are engaged in this case. It is not therefore necessary to consider Art 14. Had it been necessary, the Appeal Panel would have held that women who are contraindicated to alendronate are not a group within the meaning of Art 14, but that there will be women with certain disabilities who do constitute such a group. The Appeal Panel would have held that the guidance discriminated against such women and that such discrimination was not justified, for the reasons given under ground one above.
131. The Appeal Panel would also have held that women under 70, ages between 70 and 75, and above 75 constitute groups within the meaning of Art 14, and that the guidance discriminates between such groups. However the Panel would have held that such discrimination was justified and proportionate in pursuit of a legitimate aim, as age is a well recognised risk factor for osteoporosis and for fracture.

132. The appeal panel therefore dismissed this ground of appeal.

NOS appeal point 3.3. Inclusion of screening costs in the cost effectiveness analysis is outside the Institute's remit

133. For the reasons given at paragraphs 29 and 84 above the appeal panel dismisses this ground of appeal.

Conclusion

134. The Appeal Panel upholds this appeal under Ground 1 (paragraphs 20, 35, and 63), and makes no findings in regard to aspects of Ground 2 (paragraph 81) and Ground 3 (paragraph 116). The Appeal Panel rejects the appeals on all other points.

135. The Panel requests the Guidance Executive to:

- a) refer this appraisal to the Appraisal Committee with the request that it provides guidance on the use of etidronate, risedronate, raloxifene and strontium ranelate in the primary prevention of osteoporosis, based on their clinical and cost effectiveness, for patients in whom alendronate is contraindicated, poorly tolerated or ineffective.
- b) request permission from the World Health Organisation (see paragraph 32) to release the Institute from its undertakings relating to the academic-in-confidence data used to populate the economic model underpinning this appraisal. If this request is met, then the consultees should be provided with a read-only copy of the economic model.
- c) improve the clarity of the FAD by:
 - amending the guidance section (paragraph 80) so that health professionals can more readily understand the circumstances when particular products are appropriate for use in the NHS;
 - including appropriate explanations about the time-frames over which the economic model estimates the longer benefits of the products (paragraph 44); and the reasons for

accepting differential incremental cost effectiveness ratios in determining the appropriateness of use of these products for primary and secondary prevention (paragraph 96).

136. 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.