

# 1 Guidance (outcome from November 2006 Committee meeting discussion on alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women)

This guidance covers the use of alendronate, ~~etidronate~~, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women who have osteoporosis, but who have not sustained a clinically apparent osteoporotic fracture.

This guidance covers the treatment of postmenopausal women who have normal levels of calcium and vitamin D. Unless clinicians are confident that women who receive osteoporosis treatment have an adequate calcium intake and are vitamin D replete, calcium and/or vitamin D supplementation should be considered.

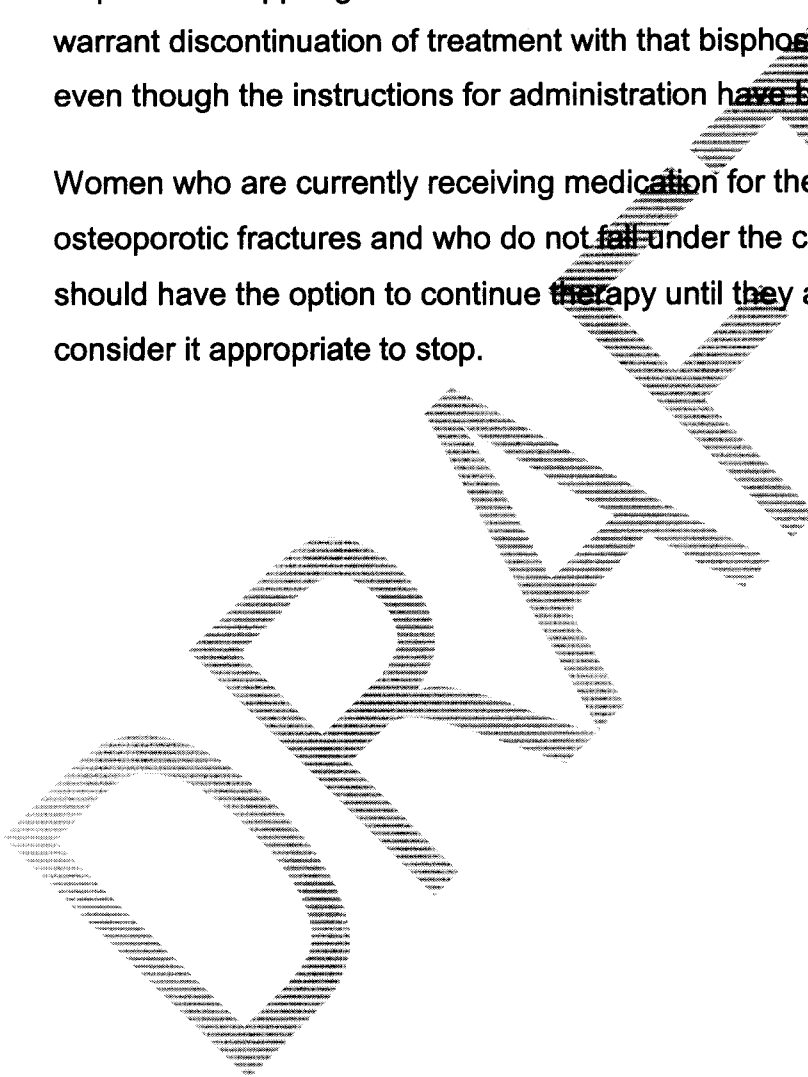
This guidance ~~does not cover the use of these drugs for the primary prevention of osteoporotic fractures in women with normal bone mineral density (BMD) or with osteopenia, that is, women with a T-score that is higher than -2.5 SD. Recommendations related to women with osteopenia will be covered within a NICE clinical guideline on osteoporosis.~~

This guidance ~~does not cover the use of these drugs for the primary prevention of osteoporotic fractures in women who are on long-term systemic corticosteroid therapy. Recommendations related to women who are on long-term systemic corticosteroid therapy will be covered within a NICE clinical guideline on osteoporosis.~~

T-score relates to the measurement of BMD using dual energy X-ray absorptiometry (DXA) scanning expressed as the number of standard deviations (SDs) from peak BMD.

- 1.1 Alendronate is recommended for the primary prevention of osteoporotic fragility fractures in women aged 70 years or older, who have one or more clinical risk factors (see section 1.6) and osteoporosis at a T-score of -2.5 SD or below. When the decision has been made to initiate treatment with alendronate, the preparation prescribed should be chosen on the basis of the lowest acquisition cost.
- 1.2 Risedronate is recommended as a treatment option in women aged 70 years or older who have one or more clinical risk factors (see section 1.6) and osteoporosis at a T-score of -3 SD or below and who are contraindicated or intolerant of alendronate (as defined in section 1.7).
- 1.3 Etidronate is recommended as a treatment option under the circumstances specified in section 1.2. However, clinicians and patients need to balance the drug's overall proven effectiveness profile against tolerability and adverse effects in individual patients.
- 1.4 Strontium ranelate is recommended as a treatment option for women aged 70 years or older who have one or more clinical risk factors (see section 1.6) and osteoporosis at a T-score of -4 SD or below and:
  - for whom bisphosphonates are contraindicated (see Summaries of Product Characteristics)
  - or
  - who are unable to comply with the special instructions for the administration of bisphosphonates
  - or
  - who are intolerant of bisphosphonates (as defined in section 1.7).
- 1.5 Raloxifene is not recommended as a treatment option for the primary prevention of osteoporotic fractures.

- 1.6 For the purpose of this guidance, clinical risk factors to be considered are: parental history of hip fracture; low body mass index (defined as less than 22 kg/m<sup>2</sup>); alcohol intake of 4 or more units per day; and medical conditions associated with low BMD.
- 1.7 For the purpose of this guidance, intolerance of a bisphosphonate is defined as persistent upper gastrointestinal disturbance that is sufficiently severe to warrant discontinuation of treatment with that bisphosphonate and that occurs even though the instructions for administration have been followed correctly.
- 1.8 Women who are currently receiving medication for the prevention of osteoporotic fractures and who do not fall under the criteria listed above should have the option to continue therapy until they and their clinicians consider it appropriate to stop.



### **4.3 Consideration of the evidence**

4.3.1 The Committee reviewed the data available on the clinical and cost effectiveness of alendronate, etidronate, risedronate, raloxifene and strontium ranelate, having considered evidence on the nature of the condition and the value placed on the benefits of these drugs by people with osteoporosis, those who represent them, and clinical experts. It also considered the consultation comments received in response to the appraisal consultation documents and the extra analysis undertaken by the NICE Decision Support Unit. It remained mindful of the need to ensure that its advice took account of the effective use of NHS resources. The Committee was aware of a previous decision of the National Screening Committee not to recommend screening to prevent osteoporotic fracture because of concerns about the accuracy of BMD assessment for the prediction of fracture and because there was no trial evidence indicating that such screening would reduce the incidence of fractures.

4.3.2 The Committee considered the clinical effectiveness data for the bisphosphonates (alendronate, etidronate, risedronate), strontium ranelate and raloxifene. It noted that all these drugs have proven efficacy in the reduction of vertebral fragility fractures for women with osteoporosis, but there were differences between the drugs as to the degree of certainty that a reduction in hip fracture resulted from treatment (considered a crucial goal in osteoporosis management). In the case of alendronate and risedronate, the Committee accepted that there was sufficiently robust evidence to suggest a reduction in hip fracture. However, the Committee noted that the available RCTs for etidronate were of insufficient size to show statistically significant reductions in hip fracture, but that observational data lent support to an effect on hip-fracture risk.

4.3.3 The Committee noted that strontium ranelate was effective in preventing vertebral and pooled non-vertebral fractures, and the drug resulted in a non-significant reduction in hip-fracture incidence. The

Committee was also aware of the result of a post-hoc subgroup analysis showing a statistically significant reduction in the incidence of hip fractures in women over the age of 74 years who had a T-score of -2.4 SD or below.

4.3.4 The Committee noted that the evidence for raloxifene did not show an effect on hip fractures but that there was evidence for a beneficial effect of raloxifene on the incidence of breast cancer.

4.3.5 The Committee noted that fracture risk is clearly related to age, low BMD and previous fracture. The Committee accepted that most of the risk factors identified by the WHO study (see section 4.2.12) were likely to be associated with an increased fracture risk, which is partially independent of BMD. However the Committee was not persuaded that the risk factor 'current smoking' was statistically significant in women. The Committee noted that alcohol consumption is a statistically significant risk factor at 4 units per day and above. The Committee further noted that a full review of other risk factors is being carried out as part of the development of the clinical guideline on osteoporosis.

#### **Cost-effectiveness modelling**

4.3.6 Because women who have not had a fracture would not normally present to clinicians, the Committee considered it necessary to consider the cost involved in the assessment of fracture risk and DXA scanning in its appraisal of the drugs for the primary prevention of osteoporotic fractures.

4.3.7 The Committee acknowledged the efforts of the Assessment Group to build on the model used previously. The Committee noted that it combined trial data on drug effectiveness, with the so-far unpublished and complex WHO data to apply these to women's fracture risk. The Committee was concerned that there was not sufficient evidence for a proven treatment effect on fracture risk related to independent risk factors other than low BMD, age and prior fracture (see section 4.3.5). With this caveat in mind, the Committee concluded that the

Assessment Group's model was a useful basis for exploring the estimates of cost effectiveness; it used data for a wide age range (age 50–75 years and over) and was updated to use all fracture sites, more recent utility, prevalence and risk-factor data, and an adjusted prevalence of fractures in the average population. Although the Assessment Group's model considered a shorter time period (10 years) than the manufacturers' models, the Committee thought that this was appropriate considering the age groups involved and the uncertainties around health effects over a longer period.

4.3.8 The Committee discussed the assumptions underpinning the most recent economic modelling undertaken by the Assessment Group. It noted that some of the uncertainties surrounding the results of the previous modelling had been partially explored by the inclusion of assumptions relating to the costs and disutility associated with treatment-related side effects and with non-persistence with therapy in a proportion of patients. The Committee also noted the effect of the recent price reductions for generic alendronate (70 mg weekly dose) on the base case of cost effectiveness for this form of the drug.

4.3.9 The Committee considered the base-case assumptions and those in various additional analyses. The Committee noted that the fracture costs used in the base-case analysis were those used in the original assessment report developed in 2002 and considered that these were likely to be outdated. The Committee agreed that costs based on Health Resource Groups, including home help costs, were likely to provide the most accurate reflection of the cost of fractures to the NHS and personal social services, and it decided to incorporate these costs into the base-case analysis.

4.3.10 The Committee considered the utility multiplier for the first year after a vertebral fracture used in the base-case analysis and noted that it was considerably worse than that for a hip fracture. Although the Committee acknowledged that vertebral fracture can lead to greatly reduced quality of life, it considered that it was not likely that this would

so greatly outweigh the utility decrement associated with a hip fracture. Therefore, the Committee considered it reasonable to assume that the disutility in the first year after a vertebral fracture was equivalent to the disutility in the first year after a hip fracture and decided to include this assumption in the base-case analysis.

4.3.11 The Committee was not persuaded that the drugs under consideration had been unequivocally shown to reduce fracture risk that was attributable to risk factors not mediated through BMD. Therefore, analyses using assumptions of 0% and 50% efficacy on fractures associated with risk factors other than age and low BMD were considered. The Committee noted the impact of these analyses on the cost-effectiveness estimates. The Committee concluded the uncertainty surrounding the efficacy of the drugs on risk factors not mediated through low BMD should be factored into its decision making.

4.3.12 The Committee discussed the possibility that both the disutility associated with side effects of bisphosphonates and the proportion of people who experience these side effects may exceed the model's assumptions. The Committee noted that the modelling of side effects had been based solely on patients who report their side effects to their GP. The Committee noted the analysis in which the model's small disutility for side effects was multiplied by 10. The Committee concluded that the uncertainty surrounding this assumption should be factored into its decision making.

4.3.13 The Committee also discussed other issues relevant to its recommendations, not represented in the model, that may have had an impact on the cost-effectiveness estimates. These included: possible long-term adverse effects of bisphosphonates on the formation of new bone; the probability that more GP time would be involved in identifying women with risk factors associated with osteoporosis; and the likelihood that DXA scanning outside a clinical trial environment would not be undertaken as accurately as in the clinical trials. Although a quantitative analysis of the uncertainties surrounding these issues was

not available, the Committee agreed that these issues should be factored into its decision making. It concluded that it was likely that these uncertainties could be approximated through the sensitivity analysis for side effects described in section 4.3.12.

### **Bisphosphonates – alendronate**

4.3.14 The Committee considered the results of the economic model in terms of the price reduction for generic alendronate and the newly included assumptions (see sections 4.3.8 to 4.3.11) and observed that, for generic alendronate, identification and treatment strategies could be considered cost effective in women with osteoporosis aged 65 years and over. However, the Committee was mindful of the uncertainties presented by a number of the analyses and other factors that were not included in the economic model (see sections 4.3.12 and 4.3.13). This led the Committee to conclude that generic alendronate would constitute an appropriate use of NHS resources for postmenopausal women with osteoporosis who were aged 70 years and over. The Committee further considered that the adoption of such a strategy would result in very many women (that is, all women aged over 70 years visiting their GP for any reason) being referred for DXA scanning, who may be well and asymptomatic but also not at high risk of fracture. Therefore, the Committee agreed that treatment with alendronate should be considered only in women with at least one clinical risk factor, and that a DXA scan be carried out to confirm osteoporosis.

4.3.15 Having reviewed the evidence on risk factors and the views of the clinical experts, the Committee agreed that the appropriate clinical risk factors indicating a high probability of low BMD should be: parental history of hip fracture; low body mass index (defined as less than 22 kg/m<sup>2</sup>); alcohol intake 4 units per day and above, and medical conditions associated with low BMD (as listed in section 2.11).



4.3.16 The Committee noted the very different prices of different versions of alendronate. Because of its much lower price, generic alendronate is always more cost effective than branded alendronate. Therefore, the Committee concluded that alendronate must be prescribed on the basis of the lowest acquisition cost available to the NHS.

### **Bisphosphonates – risedronate and etidronate**

4.3.17 The Committee noted that risedronate was less cost effective than generic alendronate because of the substantial difference in acquisition cost. It concluded that risedronate could not be recommended as a first-line treatment, but that the drug could only be recommended for women with a greater degree of osteoporosis and who were also contraindicated to, or intolerant of, alendronate. The Committee observed that the identification costs associated with finding women who could be cost-effectively treated with risedronate would be negligible, because women suitable to receive it would have already undergone an assessment and had a DXA scan in order to be assessed for first-line treatment with alendronate. Therefore, the Committee decided that risedronate should be an option for women aged 70 years or older with a clinical risk factor and a T-score of -3 SD or less who were contraindicated to, or intolerant of, alendronate. The Committee was aware that this reduced the treatment options for women with a T-score between -2.5 and -3 SD who were contraindicated to, or intolerant of, alendronate. However it was convinced that treating this group with risedronate was not an efficient use of NHS resources.

4.3.18 In view of its concerns surrounding the evidence base for etidronate, and taking into account the views of clinical experts and consultees, the Committee decided that etidronate should not be recommended in preference to alendronate and risedronate, but that on the basis of its cost effectiveness it could be used as an alternative treatment option for women aged 70 years or older with a clinical risk factor and a T-score of -3 SD or less who were contraindicated to, or intolerant of,

alendronate with the note that, in deciding between risedronate and etidronate, clinicians and patients need to balance the drugs' overall effectiveness profile against tolerability and adverse effects in individual patients.

### **Strontium ranelate**

4.3.19 The Committee noted that strontium ranelate was less cost effective than bisphosphonates and was indeed likely to be dominated in terms of cost effectiveness by bisphosphonates. Therefore, the Committee concluded that strontium ranelate should be an alternative treatment option for women at relatively high fracture risk, for whom bisphosphonates are contraindicated, or who are unable to comply with the special instructions for the administration of bisphosphonates, or who cannot take them because of intolerance. The identification costs associated with finding women who could be cost-effectively treated with strontium ranelate would be negligible because women suitable to receive it would have already undergone risk assessment and had a DXA scan in order to be assessed for first-line treatment with alendronate. Therefore, the Committee agreed that strontium ranelate should be recommended in women aged 70 years and older with at least one clinical risk factor and a T-score of -4 SD or below who could not take bisphosphonates because: bisphosphonates were contraindicated; or the women could not comply with the instructions for treatment with bisphosphonates; or they were intolerant of bisphosphonates. The Committee agreed a definition of bisphosphonate intolerance as: persistent upper gastrointestinal disturbance that is sufficiently severe to warrant discontinuation of treatment with a bisphosphonate and that occurs even though the instructions for administration have been followed correctly. Again, the Committee was aware that this reduced the treatment options for women with a T-score between -3 and -4 SD who were intolerant of bisphosphonates. However, it was convinced that treating this group with strontium ranelate was not an efficient use of NHS resources.

## Raloxifene

4.3.20 The Committee discussed the reported benefits of raloxifene on breast cancer risk. It heard from the experts that the possibility of preventing vertebral fractures and breast cancer simultaneously could be attractive particularly to younger postmenopausal women. The Committee also heard from the experts that evidence on the effect of raloxifene in reducing cardiovascular risk is not considered to be robust and, furthermore, there is some concern over the increased risk of VTE (see section 4.1.9.3).

4.3.21 The Committee noted that a higher proportion of the overall benefit associated with raloxifene was attributable to its effect on the prevention of breast cancer than to its effect on the prevention of osteoporotic fractures. The Committee agreed that, in principle, the side effects of using a technology should be considered, but there were a number of reasons why the Committee considered that the breast cancer benefit should not be the sole factor in deciding whether raloxifene is a cost effective option for the treatment of osteoporosis, in particular:

- From the evidence presented, raloxifene was not as effective as bisphosphonates for treating osteoporosis.
- Raloxifene's effect on the prevention of breast cancer has not been assessed by the regulatory authorities.

4.3.22 The Committee observed that the cost effectiveness of raloxifene, in terms of fracture prevention, was very unfavourable relative to the bisphosphonates and strontium ranelate. The benefits of raloxifene's breast cancer effect were in any case noted to be most valuable in younger women rather than in the population for whom primary prevention of osteoporotic fractures could be considered cost effective. On balance, the Committee concluded that raloxifene should not be recommended as a treatment option for the primary prevention of osteoporotic fragility fractures in postmenopausal women.

4.3.23 The Committee also considered women currently receiving alendronate, etidronate, risedronate, strontium ranelate or raloxifene for the prevention of osteoporotic fractures and concluded that they should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

#### **Calcium and vitamin D prerequisites for treatment**

4.3.24 The Committee discussed the effect of calcium and vitamin D on the clinical effectiveness of the drugs considered. In the studies that formed the basis of this appraisal, all participants were said to have adequate calcium and vitamin D levels. The Committee appreciated that the general population, particularly the elderly population, cannot be assumed to have adequate dietary intake of calcium and vitamin D. It was also considered important to note that adequate levels of calcium and vitamin D are needed to ensure optimum effects of the treatments for osteoporosis. The Committee concluded that calcium and/or vitamin D supplementation should be provided unless clinicians are confident that women who receive osteoporosis treatment have an adequate calcium intake and are vitamin D replete. The Committee suggested that the forthcoming clinical guideline could specify how such assessment should be made and what supplementation should be prescribed.