NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

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

Response to comments received from consultees and commentators that specifically relate to the SECONDARY prevention Appraisal Consultation Document (2006 ACD) – Please see the PRIMARY prevention 2006 ACD for general comments.

Consultee or Commentator	Comment	Institute Response
Manufacturer		
Alliance for Better Bone Health	**2. Recommended revision** *The Alliance proposes that the guidance recommends the use of oral bisphosphonates for specific patient populations as first line treatment options for the prevention of osteoporotic fractures and that, when the decision has been made to prescribe a bisphosphonate, it is recommended that therapy should usually be initiated with a drug with a low acquisition cost.* To address the difficulties presented by the current provisional recommendations, outlined above, the Alliance proposes that they are revised as follows: ***Secondary prevention:*** • Oral bisphosphonates are recommended as first line treatment for the primary prevention of osteoporotic fragility fractures in women aged 75 years or older, without the need for DXA scanning; aged 65–74 years if a T-score of -2.5 SD or below is confirmed by DXA scanning; and aged below 65 years if they have a very low BMD (that is, a T-score of approximately -3 SD or below). • When the decision has been made to prescribe a bisphosphonate, it is recommended that therapy should usually be initiated with a drug with a low acquisition cost (taking into account the required frequency, dose and product price per dose). • If the woman is unable to tolerate, cannot comply with special instructions for administration or does not make progress with the initial bisphosphonate, treatment with other suitable bisphophonates should be considered before initiating treatment with another class of drugs. We have no specific requests for changes to the wording of Sections 1.4-1.7 of the primary prevention guidance and 1.4-1.9 of the secondary prevention guidance, although these sections would also benefit from simplification.	Comment noted. The 2007 ACD gives recommendations only for the initiation of secondary prevention therapy and do not cover the treatment of women who, for whatever reason, have withdrawn from initial treatment. The NICE clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' will address 2nd line treatment options. Comment noted.
Eli Lilly	**Secondary Prevention** i. For secondary prevention we believe that all the relevant evidence was supplied and available to the	Comment noted.

Consultee or Commentator	Comment	Institute Response
	Appraisal Committee. **Raloxifene** We continue to be dissatisfied that raloxifene remains in third line position after bisphosphonates and strontium ranelate. The clinical data for strontium is recognised as not being not as robust as for the bisphosphonates, and it is still an unproven therapy in clinical practice. Raloxifene has been available for many years and hence its efficacy and safety in clinical practice are well established. It is noted that the cost effectiveness of raloxifene is not as strong as for bisphosphonates and strontium if the breast cancer benefit is not taken into account. However, when the breast cancer benefit is taken into account, the cost effectiveness of raloxifene is better than for strontium in almost all severities and age bands. We therefore would argue that raloxifene is at least given equal status with strontium in the guidance. We are again concerned that the application of an arbitrary £20,000 per QALY threshold has excluded some patients from treatment with raloxifene. **Teriparatide** In October 2004 one of the main grounds of Lilly's Appeal against the Secondary Prevention FAD (which became NICE Guidance 87) was that there was a group of patients who were younger than 65 years but who had a clinical need for teriparatide. Although this was rebutted by NICE at the time, we are please that this has now been recognised in the current ACD. i. The clinical and cost effectiveness summaries are reasonable interpretations of the evidence except for the continued omission of inclusion of the breast cancer benefit for raloxifene, and our concern regarding the application of the arbitrary £20,000 per QALY threshold in the economic analysis. i. On the basis of our comments above we <u>do not</u> consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS.	The 2007 ACD gives recommendations only for the initiation of secondary prevention therapy and do not cover the treatment of women who, for whatever reason, have withdrawn from initial treatment. The NICE clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' will address 2nd line treatment options.
Nominated patient experts and clinical specialists		
Professor Juliet Compston Clinical Expert	**Secondary prevention ACD: specific comments** 1. As noted above, inclusion of the assumption of zero efficacy for the contribution of clinical risk factors to fracture risk is incorrect and should be removed. 2. It is stated that the guidance does not cover the treatment of women with other medical conditions	1.This has been amended in the 2007 ACD. 2. The fact that the guidance does not

Consultee or Commentator	Comment	Institute Response
	associated with low BMD or who are on long-term (undefined) glucocorticoid therapy. This means that a substantial number of women with osteoporotic fragility fractures will be excluded from the guidance (see section 2.11). For example, a woman who had had an untreated premature menopause and presented at age 80 with a hip fracture would not be considered eligible for treatment under the current recommendations.	cover long-term glucocorticoid therapy does not exclude treatment. The guideline is expected to cover this patient group. Note also that the 2007 ACD states that woman over the age of 75 with a fracture does not necessarily need to have her BMD assessed to be eligible for treatment.
	3. The recommendation that etidronate should be used as the first alternative treatment option to alendronate is based purely on cost-effectiveness and ignores the lack of proven efficacy of etidronate against non-vertebral and hip fractures. Many of those individuals unable to take alendronate will be the frail and elderly who are at high risk of these fractures. To recommend a drug with no evidence for efficacy against these fractures is at odds with the Institute's remit to consider both cost-effectiveness and clinical effectiveness.	3. The Committee has taken into account the reservations of consultees and commentators regarding the clinical effectiveness of etidronate. Therefore, the Committee has made the recommendation in the 2007 ACD that etidronate is no longer an option for the initiation of secondary prevention therapy.
	4. The use of more stringent intervention criteria for drugs other than alendronate and etidronate means that some women who are told that they need treatment will later be told that they cannot continue with treatment. This poses significant ethical problems for physicians and other healthcare professionals that are not addressed in the ACD. It will also undoubtedly cause distress to patients. Moreover, some women aged over 75 years will have to have BMD measurement if there is a need to change treatment. Again, this is likely to occur mostly in the frail and elderly population, in whom it is often impracticable to do bone density measurements (assuming that the resources are available).	4 The 2007 ACD gives recommendations only for the initiation of secondary prevention therapy and do not cover the treatment of women who, for whatever reason, have withdrawn from initial treatment. The NICE clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' will address 2nd line treatment options.
	5. Surely, an unsatisfactory response to bisphosphonates should also be included in the recommendations for strontium ranelate and raloxifene? 6. As they stand, the complexity of the recommendations for secondary prevention would make implementation difficult if not impossible for most primary care physicians.	5. The 2007 ACD gives recommendations only for the initiation of primary prevention therapy. 6.Comment noted. The 2007 ACD is a substantial simplification.

Consultee or Commentator	Comment	Institute Response
Dr Peter Selby Clinical Expert	**Secondary prevention** 1 In addition to the problems with the hierarchical introduction of therapies after the failure of alendronate noted above I believe that the committee have been too prescriptive in their guidance regarding intolerance of bisphosphonates. Upper gastrointestinal side-effects may be the most frequent adverse event following administration of alendronate but a whole variety of other side-effects may occur causing intolerance and surely the committee is not wishing to preclude movement to any other agent following the occurrence of these. 2 In contrast to the above comment the committee should note that if a patient is unable to comply with the special instructions for the administration of alendronate then it is all but impossible that they will be able to comply with the special instructions for the administration of risedronate 3 I presume that it is merely an oversight that failure of response to bisphosphonates is not included as one of the alternative ways in which the use of strontium ranelate is sanctioned. Likewise should not failure of response to strontium ranelate be included as a means of obtaining raloxifene? 4 The definition of unsatisfactory response represents a marked improvement on that definition in current guidance.	For points 1 to 4: The 2007 ACD gives recommendations only for the initiation of secondary prevention therapy and do not cover the treatment of women who, for whatever reason, have withdrawn from initial treatment. The NICE clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' will address 2nd line treatment options.
Professional and Patient Groups		
British Geriatric Society	In the secondary prevention ACD, women above the age of 75 years with a fragility fracture will be allowed alendronate without a DXA scan. If they do not tolerate this, then they can only be offered risedronate if they have a DXA scan showing a T Score of -2.5 or lower. This will lead to the situation where patients are initially told that they need alendronate to prevent further fractures, but are then subsequently informed that they are not bad enough to warrant risedronate if they experience side-effects with alendronate. Similarly in the primary prevention ACD, if a woman with a clinical risk factors has a T Score of -2.5 or lower, she will be offered alendronate, but if she fails to tolerate this (or etidronate), she will be unable to have risedronate if her T Score is between -2.5 and -2.9 or strontium ranelate if the T Score is between -2.5 and -3.9. The progressively more restrictive T Score thresholds to progress down the treatment options will be difficult to implement in clinical practice and will inevitably cause tension in the doctor-patient relationship. The position of raloxifene in the secondary prevention ACD is also difficult to justify, in that its use will be limited to women who have been unable to take or tolerate bisphosphonates and strontium ranelate, with more restrictive T Score thresholds in younger women. It will therefore only be given to younger women with marked osteoporosis (T Score of -3.5 under the age of 65 years) or older women above the age of 75 years with a T Score of -2.5 or lower. In both these situations, there is a significant risk of non-vertebral fractures, which raloxifene has not been shown to prevent.	The 2007 ACD gives recommendations only for the initiation of secondary prevention therapy and do not cover the treatment of women who, for whatever reason, have withdrawn from initial treatment. The NICE clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' will address 2nd line treatment options.

Consultee or Commentator	Comment	Institute Response
	I am concerned that in the secondary prevention ACD, a woman under the age of 65 years who already has a low trauma fracture and documented osteoporosis, will be denied effective treatment, unless the T Score is -3.0 or lower. TAG 87 previously allowed treatment if the T Score was between -2.5 and -3.0, if there was an additional risk factor present. This will be particularly hard to explain and justify in women with a symptomatic vertebral fracture, where there is a 20% risk of further fracture in the subsequent year (Lindsay et al, JAMA. 2001; 285: 320-323). I welcome the widening of the criteria for the use of teriparatide in the secondary prevention of osteoporotic fragility fractures in younger women aged 55–64 years, if they have a T Score of -4.0 or lower and multiple fractures. I am also pleased that the Appraisal Committee has modified their definition of unsatisfactory response to treatment, so that it no longer requires documentation of a decline in bone density. This is particularly relevant in older women above the age of 75 years, where unsatisfactory response could not be demonstrated previously, as a baseline DXA scan was not advocated.	The age at which therapy can be initiated has been revised following the comments received. Comment noted.
Institute for Ageing & Health	5. **For secondary prevention of fracture** in osteoporosis, I have concerns that the evidence base is flawed. The studies used in the appraisal are the same as for primary prevention of fracture. However, the clinical scenario is very different. I agree that it is likely that the threshold for treatment is much lower, than for primary prevention of fracture. There is insufficient data presented on the WHO model used. Was this modelling fracture risk post-fracture or based on BMD? a. There is implicit rationing of DXA scanning as women aged 75+ get bisphosphonate therapy without a scan b. Etidronate cannot be advocated for this indication! c. Unlike primary prevention, strontium can be used with a similar threshold as bisphosphonate therapy d. Women aged 75+ are unlikely to get teriparatide, as they are unlikely to get DXA scanning (see5a)	a) Comment noted b) The Committee has taken into account the reservations of consultees and commentators regarding the clinical effectiveness of etidronate. Therefore, the Committee has made the recommendation in the 2007 ACD that etidronate is no longer an option for the initiation of primary prevention therapy. c) and d) The 2007 ACD gives recommendations only for the initiation of secondary prevention therapy and do not cover the treatment of women who, for whatever reason, have withdrawn from initial treatment.
Royal College of Nursing	**Secondary Prevention of Osteoporosis in Post menopausal women.** The Royal College of Nursing welcomes the work and extensive review undertaken for this technology	Comment noted.

Consultee or Commentator	Comment	Institute Response
	appraisal but again raises some concerns and queries on some of the recommendations.	
	We find it hard to accept that the unfortunate people who develop osteoporosis and are below 65 years of age will not receive treatment – although we do not have enough data or knowledge of the economic model over the long term – the rationale appears flawed if we leave treatment until a much later stage and risk them not being appropriately picked up for treatment in later life. A particular concern are those who have surgical procedures that render them at risk (e.g. hysterectomy and oophorectomy) and are poorly advised/managed or have strong family or medical history risk factors, fracture and then finally get some treatment options.	In the 2007 ACD, The age at which therapy can be initiated has been revised following the comments received.
	Those that are intolerant or unable to take oral bisphosphonates must have other treatment options available to them - provided they are also provided with appropriate nurse/pharmacist/medical support to understand their treatment and rationale/risks and advice on administration etc.	The 2007 ACD gives recommendations only for the initiation of secondary prevention therapy and do not cover the treatment of women who, for whatever reason, have withdrawn from initial treatment.
	Etidronate is no longer widely used as it has been superseded by the newer generation of bisphosphonates in both effectiveness and ease of use. Many patients who take a once weekly preparation, would not wish to return to the regimen for taking Etidronate.	The Committee has taken into account the reservations of consultees and commentators regarding the clinical effectiveness of etidronate. Therefore, the Committee has made the recommendation in the 2007 ACD that etidronate is no longer an option for the initiation of primary prevention therapy.
	There should be some form of algorithm to aid practitioners when individuals are identified with particular high risk factors (or BMD scoring issues) that should allow a more expensive yet more effective therapy to be offered based upon sound clinical judgement.	Comment noted.
	In the area of compliance and side effects, again there is the omission of a strategy to assess compliance, management should include the CNS.	The issue of managing compliance may be addressed by the clinical guideline for osteoporosis.
	With regard to calcium and vitamin D, we consider that a universal assessment within the clinical guideline is an excellent move forward.	Comment noted.
	We would welcome the introduction of a fracture risk prediction tool (which John Kanis is developing with WHO) and wonder if it would influence the way patients are assessed and treated.	Comment noted.
Society & College		

<table>
<tr><th>Consultee or Commentator</th><th>Comment</th><th>Institute Response</th></tr>
<tr><td>of Radiographers</td><td>Turning to the secondary prevention of osteoporotic fracture appraisal document, we find that this is far too complicated in the scenarios concerning when and what treatment might be offered once a fracture has occurred. In our view it has too many sections of thresholds, with and without concomitant risk factors and ever changing levels of Bone Mineral Density. There is a risk that all those concerned are going to be confused about prescription recommendations. We fear that this will result in inappropriate treatment choices or no treatment at all.</td><td>The 2007 ACD gives recommendations only for the initiation of secondary prevention therapy and do not cover the treatment of women who, for whatever reason, have withdrawn from initial treatment</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td colspan="3">Southwark PCT</td></tr>
<tr><td></td><td>Southwark Primary Care Trust generally agrees with the ACD and has outlined our comments below.

<table><tr><th>Headings</th><th>Comments</th></tr><tr><td>Secondary prevention</td><td>• Our response is the same as for primary prevention
• Unclear as to why the NICE Technological Appraisal guidance 87 contained a chapter on “Implications for the NHS” but ACD for primary and secondary prevention did not.
• Calcium and Vitamin D supplementation. Unclear as to why the language changed from provided in TA 87, January 2005 to considered in the ACD.</td></tr><tr><td>Other comments</td><td>Use of language.
1.3,1.4, 4.1.12.4,4.3.21,4.3.19,4.3.22 uses comply while adhered to is used in 1.7. The preferred choice is adhered to
3.6 “Specific instructions” is preferred to “complex instructions” &” special instructions” in 4.3.19,4.3.21</td></tr><tr><td>Consistency</td><td>3rd point of 1.1 Should read post menopausal and below 65 as in 1.3</td></tr></table></td><td>Please refer to the response in the primary prevention comments table.

The text has been edited to improve clarity.

The word persistence has been used

The 2007 ACD recommendations have been revised in that all postmenopausal women are included.</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td colspan="3">NHS Quality Improvement Scotland</td></tr>
</table>

Consultee or Commentator	Comment	Institute Response
	Reviewer 2. **i) Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate.** The stance on this in the Secondary Prevention guidance has clearly softened compared with before in that 4.3.10 suggests that there is still a role for DXA scanning in patients over age 75 after fracture. The evidence does not support the assertion made that "it is very likely that women who have sustained a fragility fracture will have a low BMD (T-score of -2.5 or below). Our own data shows that only around 60-65% of this population have a BMD of <-2.5. **Reviewer 3.** Furthermore, for secondary prevention, although a CPQ of £30,000 was considered when modelling for alendronate, for all of the other drug treatments the cut off was set at £20,000/QALY and higher CPQs were again not even considered. In earlier ACDs higher CPQ were considered (and indeed accepted in TA 87). No explanation for this inconsistency is provided and again it does not reflect NICE's procedures. A clear moving of the goal posts is demonstrated by these changes and this requires proper justification; this is lacking from the ACDs. *"T-score measurements vary by site and method. It has been recommended that BMD should be measured at the femoral neck and/or lumbar spine using DXA to estimate fracture risk and that treatment decisions should be based on the lowest value".* The NOS has begun to try to develop algorithms from this guidance which would allow clinicians to follow the recommendations in practice. However, in particular for the guidance on secondary prevention of osteoporotic fractures, it is almost impossible to produce a clinically useful tool.	In the 2007 ACD, the Committee recommends for secondary prevention that for women age 75 years or older a DXA scan may not be required if the responsible clinician considers it to be clinically inappropriate or unfeasible This was a misunderstanding and the 2007 ACD has been amended to improve clarity. Comment noted.