

GDG Response to Osteoporosis ACDs April 2008

The comments in this document are the considered response of the NICE osteoporosis guideline development group (GDG), NICE's other advisory body, that is developing guidance in parallel with these technology appraisals.

Much of this response draws on the clinical expertise of key people in the osteoporosis field, all of whom are practising clinicians, specialist pharmacists or patient representatives. Under conditions of parallel development, the GDG has a responsibility to share its clinical expertise with the Committee in order that the appraisal recommendations are clinically meaningful and possible to implement, to the benefit of patients and the NHS.

The GDG did not welcome the outcome of the appeal hearing inasmuch that the Committee, rather than the GDG, is now required to make recommendations for second-line treatments. This is an area that requires great clinical understanding and the GDG is concerned that the Committee is inexperienced in work of this nature. Therefore it is vital that the comments in this document are treated seriously.

We address three main issues in this response:

- Firstly, the GDG is concerned about the medical ethics and clinical manageability of the ACD recommendations for second-line treatment; that is, giving a woman alendronate because she is at risk of osteoporotic fracture, and then, if she is intolerant of the drug, being forced to tell her that she can have no other drug until her risk increases. We consider how these neglected clinical and ethical issues can be quantified and translated into more appropriate recommendations for practice
- Secondly, the GDG doubts whether the clinical community will be able to cope with the complexity of the ACD recommendations, as they stand, and suggests that implementation will only be possible if an electronic tool is used. A prototype is considered.
- Thirdly, the GDG requests that the recommendations in the ACDs are changed so that it is obvious that they apply solely to the osteoporosis population, in order that these recommendations can be inserted into the guideline, without negating the guideline's recommendations on other populations.

1. Second-line therapies

The GDG does not consider that all of the relevant clinical evidence has been taken into account and does not consider the provisional recommendations contained in the ACDs to be sound. They do not constitute a suitable basis for the preparation of guidance to the NHS.

1.1. The problem

The GDG believes the recommendations for second-line therapies in both primary and secondary prevention are unethical and clinically unmanageable. The true clinical position has not been fully taken into account in the modelling and its interpretation.

The GDG's ethical position is this: for a patient who is suffering from osteoporosis and at risk of a potentially life threatening fragility fracture, it is unethical to refuse to treat them except with a drug that they can not tolerate, when other effective drugs are available, **unless** the risks of the second-line treatment outweigh the advantages.

In primary prevention, there are also arguments surrounding the ethics of *causing* illness in a well person. For example, the woman who has intolerable gastrointestinal side effects from a drug, along with anxiety regarding her continued risk of fracture when that drug is withdrawn with no replacement treatment.

The GDG's clinical position is, firstly, that each patient is different and when faced with drug intolerance, the clinician and patient need to work out what is the best option within certain constraints. There must be the facility for clinicians to apply their clinical knowledge to benefit the patient.

Secondly, the GDG notes that it would be extremely difficult for a clinician to deny a patient a second-line drug when the clinician is aware that, not only is the cost step to risedronate or strontium ranelate relatively small, but that the cost of these drugs is relatively low in terms of other treatments given in primary care.

This is illustrated as follows: if the only alternative drug to alendronate were teriparatide, most clinicians would think it acceptable to say to the patient, *"I'm sorry that you cannot tolerate our main drug for preventing fractures since you are at risk, but our other osteoporosis drug is extremely expensive and only suitable to be used when people have really bad osteoporosis"*.

The difficulty for clinicians in this field is that they do not find it credible that they can use this explanation if the second-line step would be to risedronate or strontium for instance.

A further point is the question of adherence to therapy: Clinicians are currently stressing the importance of patients taking and continuing to take the medication provided for osteoporosis. Indeed data (Siris) suggest that if compliance falls below 50% then no fracture benefit accrues. GDG clinicians are concerned about the impact on compliance if the message of the appraisals is that they should simply stop therapy without considering the alternatives, which are well known to most patients, in the face of an adverse reaction.

Some of these points are further illustrated in Appendix I by two examples relating to primary prevention.

In secondary prevention, GDG clinicians believe that these ethical and clinical manageability issues are even more significant because the recommendations involve refusing to treat a woman who has already had an osteoporotic fracture.

1.2. Proposed solutions

When making cost-effective recommendations for the NHS, it is necessary to attempt to model and quantify the clinical factors described above, but, so far, the GDG does not believe that they have been taken into account. The GDG therefore proposes the following:

1.2.1 For both primary and secondary prevention

At the outset, the GDG reiterates that if more appropriate parameters had been used in the model, particularly by using the side effects parameters derived from the evidence in the SchARR systematic review rather than inflating it 10-fold, there would still be a 'step' between alendronate and risedronate, but more patients would be cost-effectively treated second-line.

With respect to the position taken in the current ACDs (i.e. using 10 x side effects for alendronate), the 10 x side effects assumption is even less tenable for risedronate as a second-line treatment for three reasons:

- The ACD recommendations group together patients contraindicated to alendronate with those intolerant of it. The SPCs clearly state that the contraindications for alendronate are greater than those for risedronate.
- In their consideration of the evidence (4.3.16 primary), the Committee attempts to justify further their assumption of the 10-fold factor in the side effects, by incorporating other issues such as: the probability that more GP time would be involved in identifying women with risk factors, and the likelihood that DXA scanning outside a clinical trial environment would not be as effective as in clinical trials. These factors are not appropriate for second-line therapies as they have already been taken into account first line.
- The only justification for giving risedronate second-line to patients who are intolerant of alendronate, is that these patients may be able to tolerate risedronate instead. Therefore the side effects profile for risedronate in these patients cannot be the same as for alendronate.

Thus, the GDG proposes that for both primary and secondary prevention, the sensitivity analysis used for second-line risedronate should be 1x side effects.

1.2.2. For primary prevention only

In this section, the GDG has attempted to model the clinical picture as represented in section 1.1 and Appendix I. To do this, we have considered two types of patient (represented by Mrs Jones and Mrs Smith in Appendix I). Both groups of patients have osteoporosis and have intolerable side effects from alendronate. The patients in one group also have pre-existing anxiety or depression - which may worsen on being told they are at risk of fracture but cannot be treated – or they may be at risk of developing anxiety for the same reasons.

a) patients with side effects and osteoporosis, but without depression or anxiety

The MAICER for primary prevention has been set at £20,000, because the situation is 'an asymptomatic group of adult patients with a high number needed to treat to avoid a fracture' (section 4.3.15). According to the ACD recommendations, only those with osteoporosis may be treated with alendronate. However, for those women who have intolerable gastrointestinal side effects in addition to osteoporosis, the situation is no longer the same: the woman is no longer asymptomatic and her ill health can be considered to have been caused by the treatment. **Therefore, for these patients intolerant of alendronate the MAICER should be raised to £30,000.**

b) patients with side effects and osteoporosis, who also have depression or anxiety (or are at risk of these)

Women who have anxiety or depression, or who are considered at risk of these conditions if osteoporosis drugs are withdrawn, are likely to experience a further reduction in their quality of life if treatment is withdrawn. **The clinical workability solution is that these patients should be offered an alternative second-line treatment if the responsible clinician considers it to be clinically appropriate.**

The GDG recommends that the ACDs should take into account the factors described above for second-line drugs in primary prevention (1 x side effects for risedronate, £30k MAICER and the potential for a reduction in quality of life as a result of depression and anxiety caused or worsened by the withdrawal of treatment).

It is unclear what the combined effect these factors would be, but we note that the thresholds generally change by 0.5 SD for a MAICER of £30k (see current assessment report) and 1x side effects for risedronate has a similar effect (see assessment report January 2007). The effect of both factors needs to be determined, with the additional factor relating to anxiety taken into account as well.

1.2.3. For secondary prevention only

As mentioned in section 1.1., the ethical and clinical position regarding secondary prevention is more extreme for a number of reasons: the woman already has a fracture, with its associated pain and she has osteoporosis and intolerable gastrointestinal side effects and, arguably, a higher risk of anxiety/depression if drugs are withdrawn, because she has already had a fracture and fears another one. She also knows there is a higher risk of another fracture. In addition, there are some women with multiple fractures who are at even higher risk (both of further fracture and anxiety/depression).

As in section 1.2.2, the GDG contends that the model has not taken into account the additional decrement in quality of life because of these factors.

In addition, the intervention thresholds for second-line risedronate are likely to be too restrictive because of the assumption of 10x side effects.

Numbers of women

A further important point which is especially pertinent to secondary prevention (because of its higher T-score intervention thresholds), is to consider what proportion of women with osteoporosis treated with alendronate will not be permitted to receive risedronate second-line. This proportion depends on age and, from the ACD recommendations, the following can be determined:

- i) the over 75s do not need a DXA scan to get alendronate first-line, but the ACD recommendation implies they should have one to get risedronate or strontium ranelate. In fact, the assessment report shows it is cost effective for all over 75s with osteoporosis to receive risedronate and cost effective for those with 1 or more CRFs to receive strontium ranelate (although risedronate is more cost effective than strontium). The clinical workability solution is that all patients over 75 should be offered risedronate or strontium ranelate as alternatives to alendronate if the responsible clinician considers it to be clinically appropriate. **The GDG requests that the recommendations are modified to take this into account (i.e. all over 75s who cannot tolerate alendronate should receive risedronate or strontium ranelate without the need for a DXA scan).**
- ii) the 70-74s: the assessment report shows it is cost effective for all 70-74s with osteoporosis to receive risedronate second-line.
- iii) 65-69s: the assessment report shows the treatment threshold for risedronate to be -3.0 SD for 0, 1 or 2 additional CRFs and -2.5 SD for 3 CRFs
- iv) and so on.

From data

the number of women eligible to receive alendronate first-line, who are intolerant to alendronate but not eligible for risedronate second-line, as a proportion of all those with osteoporosis and a fracture and receiving alendronate, to be 4% (Appendix II).

Contraindication of alendronate is age dependent, which may reduce this proportion further.

Repeating the analysis using an assumption of 1 x side effects for risedronate, calculates the proportion not allowed risedronate second-line to be 3%.

Taking into account both the reduced quality of life and the small proportion of women who would not be treated second-line, **the GDG recommends that all women with a prior fracture who are intolerant or contraindicated of alendronate should be offered risedronate second-line.** The recommendations on strontium and raloxifene should also be modified accordingly.

2. Complexity of recommendations

2.1. The problem

The GDG is concerned that the recommendations in the ACDs are too complex to be readily interpreted and implemented by busy clinicians. For example, in primary prevention there are around 12 different recommendations for first-line treatment, depending on age and number of risk factors (of two types), 10 different recommendations on second-line and 10 more for third-line.

Furthermore, there are a number of discrepancies or areas needing clarification, for example:

- i) it is implied that women over 75 years, who don't need a DXA scan for alendronate, should be sent for DXA before they can receive second-line treatment
- ii) women under 65 years can receive alendronate under certain circumstances, but may not receive second-or third-line treatment at all (or not until they fracture or reach 65 years)
- iii) it is unclear what happens if a woman has rheumatoid arthritis – does this count as both an independent risk factor and an indicator of low BMD (i.e. 2 risk factors)?

Although the GDG agrees that the complexity is the correct interpretation of the evidence, it presents the clinician with an unworkable set of recommendations.

2.2. Proposed solution

The GDG is clear that the only way the ACDs' recommendations can be applied in clinical practice is for a computerised implementation tool to be developed. The NCC has produced a prototype using Microsoft Access and screen dumps of some examples are given in Appendix III. It provides a simple way of implementation (and tracking changes in a patient's treatment).

We would strongly encourage the Committee and NICE to consider this approach, as the alternative (many sets of tables) is too cumbersome to use.

3. Wording of recommendations

The GDG is conscious that the appraisals cover only part of the population at high risk of osteoporotic fracture and only some of the licensed interventions, and that the guideline covers the whole spectrum. Therefore, it is important that the wording in the appraisal recommendations does not prevent the application of guideline recommendations to these other populations. For example, primary prevention recommendation 1.1:

Alendronate is recommended as a treatment option for the primary prevention of osteoporotic fragility fractures in the following groups: women aged 70 years or older who have an independent risk factor for fracture or an indicator of low BMD and who also have a T-score of -2.5 SD or below.

This reads that women who have a T-score above -2.5SD (i.e. osteopenia and normal BMD) should not be treated with alendronate.

However, the assessment report clearly shows that it is cost effective to treat women aged 70-74 years with alendronate where their T-score ranges from -2.0 SD for no clinical risk factors (CRFs) to -0.5 SD for 3 CRFs.

The GDG is aware that the ACDs state at the outset that they relate only to postmenopausal women who have osteoporosis, but experience shows that clinicians focus solely on the recommendations. The wording in the ACDs' recommendations appears to indicate confusion between the threshold for treatment and the inclusion criteria for the ACDs' population. The GDG is required to insert the recommendations, not the appraisals' inclusion criteria, word for word into the guideline, and the current wording would make this procedure difficult. **The GDG therefore requests that this is rectified as follows:**

Recommendation 1.1 (primary prevention), by adding an asterisk as follows:

Alendronate is recommended as a treatment option for the primary prevention of osteoporotic fragility fractures in the following groups:

- *women aged 70 years or older who have an independent risk factor for fracture or an indicator of low BMD and who also have a T-score of -2.5 SD or below*.*
- *those aged 65-69 years who have an independent clinical risk factor for fracture and a T-score of -2.5 SD or below**
- *etc*

** applies only to women with osteoporosis (a T-score of -2.5 SD or below).*

In recommendation 1.2, the women intolerant of alendronate have already been determined to have osteoporosis, so it would be better to group together the inclusion criteria (primary prevention, women, postmenopausal, osteoporosis) as follows:

*Risedronate and etidronate are recommended as alternative treatment options for the primary prevention of osteoporotic fragility fractures in postmenopausal women with osteoporosis (a T-score of -2.5 SD or below):
etc*

In secondary prevention, recommendation 1.1 would better read:

Alendronate is recommended as a treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women with osteoporosis (a T-score of -2.5 SD or below)...

(or an asterisk could be used as in the proposed recommendation 1.1 for primary prevention).

In recommendation 1.2 (secondary), the GDG believes that the table is somewhat misleading for the over 70s, in that the thresholds for cost effective treatment are not -2.5 SD: these are the inclusion criteria. Therefore, this recommendation should be written as:

Risedronate and etidronate are recommended as alternative treatment options for the primary prevention of osteoporotic fragility fractures in postmenopausal women with osteoporosis (a T-score of -2.5 SD or below):

- *who are unable to comply...and*
- *who are aged 70 years or older or who have a T-score age and number of clinical risk factors for fracture as indicated in the following table:*

Then table, but without the row for 70 or older.

As noted in section 1.2.3 above, there is also a need to revise the recommendation for the over 75s in second-line treatments for secondary prevention.

As mentioned in the GDG's previous correspondence, we envisage that the drug zoledronic acid is likely to be more cost effective as second-line therapy than risedronate, and may be more cost effective than alendronate for some patients as first-line therapy. However, we do not believe that the wording of the appraisal recommendations precludes the addition of guideline recommendations on other cost effective drugs not covered by the appraisals.

Appendix I – sample case histories (hypothetical, but based on experience in general practice)

Mrs Smith and Mrs Jones both have the same score in risk factors which entitles them to alendronate but nothing else. Both get gastrointestinal symptoms as a result of taking alendronate.

Mrs Smith is a phlegmatic individual and a reluctant tablet taker. Two years previously her husband had a fatal gastrointestinal bleed following gastric symptoms as a result of taking diclofenac for his osteoarthritis.

Mrs Jones is an anxious lady with a history of depression, despite this she is helping the GP to try to persuade her feckless daughter to have her three children immunised.

She has always been anxious about her health and last year her sister was admitted to hospital after fracturing her neck of femur. She died one month later of MRSA contracted in hospital.

Mrs Smith is far more concerned about the adverse side effects of tablets than she is about her fracture risk. It would be quite reasonable to suggest to Mrs Smith that in view of the problems with the medication the best thing to do is to stop it and monitor her osteoporosis.

Mrs Jones is understandably petrified of the osteoporosis that she now knows she has. Not to allow Mrs Jones to try an alternative therapy would, in the author's opinion, be a dereliction of care sufficiently serious to justify disciplinary action.

You do not need to have spent 20 years in general practice to realise that the harm caused by not prescribing an alternative is vastly different in these two cases.

Appendix II: proportion of women not treated second-line in secondary prevention

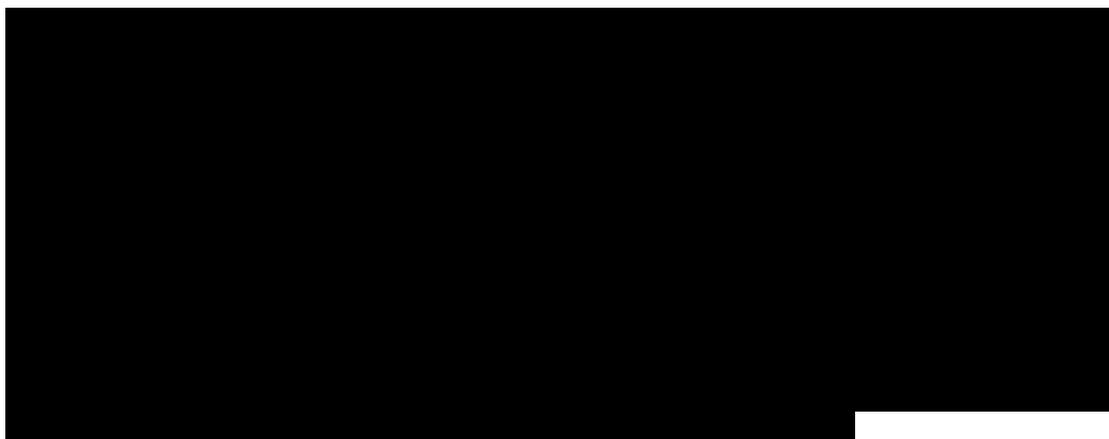


Table 1

Age	50- 55	55-59	60-64	65-69	70-74	75-79	80-84	Total
1. number with osteoporosis and a fracture	■	■	■	■	■	■	■	■
2. number with a fracture who can be treated with ALN (from ACD)	■	■	■	■	■	■	■	■
3. number with a fracture who can be treated with RSD 2 nd line (from ACD)	■	■	■	■	■	■	■	■
4. number with a fracture who can be treated with ALN but are intolerant / contraindicated of it and who can not have RSD	■	■	■	■	■	■	■	■
5. % of those with osteoporosis and a fracture, who are intolerant of ALN but can not have RSD 2 nd line	■	■	■	■	■	■	■	■
6. Number with a fracture who can be treated with SRN 3 rd line	■	■	■	■	■	■	■	■
7. % of those with osteoporosis and a fracture, who are intolerant of ALN and RSD but can not have SRN 3rd line	■	■	■	■	■	■	■	■



Table 2

Age	50- 55	55-59	60-64	65-69	70-74	75-79	80-84	Total
1. number with osteoporosis and a fracture	■	■	■	■	■	■	■	■
2. number with a fracture who can be treated with ALN (from ACD)	■	■	■	■	■	■	■	■
3. number with a fracture who can be treated with RSD 2 nd line (assuming 1x side effects)	■	■	■	■	■	■	■	■
4. number with a fracture who can be treated with ALN but are intolerant / contraindicated of it and who can not have RSD	■	■	■	■	■	■	■	■
5. % of those with osteoporosis and a fracture, who are intolerant of ALN but can not have RSD 2 nd line	■	■	■	■	■	■	■	■

Appendix III: examples of electronic tool to implement appraisal recommendations

1) Primary prevention, woman aged 71 years, 1 risk factor

a) advice for first-line

Calculation ID

No of drinks per day

Family history fracture

Prior fracture

Rheumatoid arthritis

Glucocorticoid curren

Immobility

Premature menopaus

Other conditions

No of secondary RFs

No of risk factors

Age

T score

Calculate no of risk factors

Treatment 1st line

treatment 2nd line

Microsoft Access

Primary prevention 1st line: Send for DXA and treat with alendronate if T score < -2.5 SD

OK

b) Advice for second-line

Calculation ID

No of drinks per day

Family history fracture

Prior fracture

Rheumatoid arthritis

Glucocorticoid curren

Immobility

Premature menopaus

Other conditions

No of secondary RFs

No of risk factors

Age

T score

Calculate no of risk factors

Treatment 1st line

treatment 2nd line

Microsoft Access

Primary prevention 2nd line: Treat with risedronate if T score < -3,5 SD

OK

2) **Secondary prevention, woman aged 75 years, 0 additional risk factors**
a) **advice for first-line**

The screenshot shows a clinical decision support tool interface. On the left, there is a list of input fields and checkboxes:

- Calculation ID:
- No of drinks per day:
- Family history fracture:
- Prior fracture:
- Rheumatoid arthritis:
- Glucocorticoid curren:
- Immobility:
- Premature menopaus:
- Other conditions:
- No of secondary RFs:
- No of risk factors:
- Age:
- T score:

On the right side, there are three buttons: "Calculate no of risk factors", "Treatment 1st line", and "treatment 2nd line". A "Microsoft Access" pop-up window is displayed in the foreground with the following text:

Secondary prevention 1st line: no need for DXA, offer treatment with alendronate

OK

b) **advice for second-line**

The screenshot shows the same clinical decision support tool interface as in part (a). The input fields and checkboxes are identical:

- Calculation ID:
- No of drinks per day:
- Family history fracture:
- Prior fracture:
- Rheumatoid arthritis:
- Glucocorticoid curren:
- Immobility:
- Premature menopaus:
- Other conditions:
- No of secondary RFs:
- No of risk factors:
- Age:
- T score:

The buttons on the right are also the same: "Calculate no of risk factors", "Treatment 1st line", and "treatment 2nd line". A "Microsoft Access" pop-up window is displayed in the foreground with the following text:

Secondary prevention 2nd line: Treat with risedronate if T score < -2.5 SD

OK

- 3) Primary prevention, woman aged 62 years with premature menopause and rheumatoid arthritis (which appears to be in both categories of risk factor)
- a) primary prevention

Calculation ID	<input type="text" value="1"/>
No of drinks per day	<input type="text" value="1"/>
Family history fracture	<input checked="" type="checkbox"/>
Prior fracture	<input type="checkbox"/>
Rheumatoid arthritis	<input checked="" type="checkbox"/>
Glucocorticoid curren	<input type="checkbox"/>
Immobility	<input type="checkbox"/>
Premature menopaus	<input type="checkbox"/>
Other conditions	<input type="checkbox"/>
No of secondary RFs	<input type="text" value="1"/>
No of risk factors	<input type="text" value="2"/>
Age	<input type="text" value="62"/>
T score	<input type="text"/>

Calculate no of risk factors

Treatment 1st line

treatment 2nd line

Microsoft Access

Primary prevention 1st line: Send for DXA and treat with alendronate if T score < -2.5 SD

OK

- b) secondary prevention

Calculation ID	<input type="text" value="1"/>
No of drinks per day	<input type="text" value="1"/>
Family history fracture	<input checked="" type="checkbox"/>
Prior fracture	<input type="checkbox"/>
Rheumatoid arthritis	<input checked="" type="checkbox"/>
Glucocorticoid curren	<input type="checkbox"/>
Immobility	<input type="checkbox"/>
Premature menopaus	<input type="checkbox"/>
Other conditions	<input type="checkbox"/>
No of secondary RFs	<input type="text" value="1"/>
No of risk factors	<input type="text" value="2"/>
Age	<input type="text" value="62"/>
T score	<input type="text"/>

Calculate no of risk factors

Treatment 1st line

treatment 2nd line

Microsoft Access

Primary prevention 2nd line: do not treat

OK