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 consultee, commentator and public comments on the 2007 Appraisal Consultation Document (ACD)

Consultee or Commentator	Comment	Institute Response
Manufacturer		
Eli Lilly	Thank you for the opportunity to comment on the ACD for the above appraisal. We have responded under the requested general headings but in reverse order. [In confidence data included in the comment removed] *iii) whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS.* By providing recommendations only on the 'initiation of pharmacotherapy' NICE has acted outside its remit and changed the scope of the review without consultation. We were unaware of this important change until the recent consultation. This is outside of NICE's published processes and is fundamentally wrong. It is also detrimental to patient care. Although a superficially attractive way to resolve the existing confusion between ongoing guideline and guidance processes, the decision is in fact poorly thought through. Because the proposed guidance will replace Technology Appraisal guidance no.87, but offers advice only on treatment	The letter of the 23rd February 2007 sent to Consultees and Commentators states that the Appraisal Committee focussed its preliminary recommendations for both technology appraisals on 'initiation of therapy'. The NICE clinical guideline on osteoporosis will cover the treatment of women who are contraindicated to or have withdrawn from initial treatment. There has been no change to the scope of the appraisal. Recommendations are consistent with the original DH remit[1] in that the proposed guidance provides

[1] Remit from Department of Health: To advise on the clinical and cost effectiveness of licensed treatments for the prevention and treatment of osteoporosis and prevention of osteoporotic fractures in post-menopausal women in the following pharmacological classes: Selective (o)estrogen receptor modulators (SERMs); Bisphosphonates; Parathyroid hormone (subject to licensing) relative to commonly-used treatments; and to advise if the evidence allows on how any recommended treatments could be best be targeted on those most likely to benefit.

Consultee or Commentator	Comment	Institute Response
	initiation, the suggested guidance is irresponsible and unhelpful to healthcare professionals and patients alike:	advice on the most cost-effective therapy and how recommended treatments are best targeted.
	The proposed guidance offers nothing to replace existing guidance on treatments for patients who are unable to tolerate or do not respond to alendronate, those who are contraindicated to alendronate or patients with severe osteoporosis. It makes no attempt to offer guidance on when alternatives to non-proprietary alendronate might be used in a cost effective manner. There is not even an estimated date for consultation on and publication of the clinical guideline. In the meantime lack of guidance may be interpreted as negative guidance and used by cost-conscious healthcare trusts as an excuse to reduce funding for osteoporosis in general and for some therapies in particular. The worst scenario is that patients could be denied access to useful treatments, as such we feel sure that NICE would not want to be seen endorsing a reduction in choice of therapies.	Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'. Recommendations for those intolerant or not responding to initial therapy will be covered by the clinical guideline.
	Lilly believe there is a need to provide guidance on those withdrawn from initial treatment as in the TA87 revised in the previous ACD (September 2006).	Advice on withdrawal from initial therapy and second line treatment of people with osteoporosis will be considered within the forthcoming clinical guideline.
	This decision appears to be motivated by the availability of generic alendronate and cost containment rather than providing assistance to those managing the disease in the NHS.	NICE technology appraisals contain recommendations on the clinical and cost effectiveness of technologies and NICE Clinical guidelines make recommendations on managing a disease in the NHS
	We are disappointed that NICE has spent 5 years to develop the guidance only to reduce its guidance to "start with the generic" and not suggest any further treatment algorithms. The large	Treatment options for women who are contra-indicated to

Consultee or Commentator	Comment	Institute Response
	number of drafts published to date has only increased confusion as to best clinical practice, and unfortunately the current proposal does nothing to resolve this.	alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'. Recommendations for those intolerant or not responding to initial therapy will be covered by the clinical guideline.
	As such we believe this is not sound and does not constitute a reasonable or satisfactory replacement for TA87. Either the guidance from the September 2006 ACD (which included advice for patients withdrawn from initial treatments or with severe osteoporosis) should be reinstated in light of the comments we provided during the last consultation *or* this guidance should be considered new guidance and TA87 should remain in force.	Advice on withdrawal from initial therapy and second line treatment of people with osteoporosis will be considered within the forthcoming clinical guideline.
	ii) 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 summary of the evidence in the proposed guidance is in line with the much narrower revised scope. However, the document offers no guidance on when teriparatide or raloxifene might be cost-effective treatment options. The appraisal committee is offering no interpretation in this area, despite 5 years of detailed analysis.	The Committee considered the evidence for teriparatide and raloxifene and concluded that they are not a cost effective use of NHS resources for the initiation of secondary prevention of osteoporosis (see sections 4.3.19 – 4.3.23 of the FAD).
	The failure to offer guidance on alternative therapies, is likely to result in decreased access to medicines in patients for whom they may be cost-effective, and more variability between trusts, which would be an inefficient use of NHS resources.	Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis:

Consultee or Commentator	Comment	Institute Response
		assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
	We continue to maintain that the breast cancer benefit of raloxifene is of relevance in any assessment of its cost effectiveness. Raloxifene with the full economic consequences of avoided cases of breast cancer was cost effective compared to proprietary alendronate in younger women, and may remain cost effective against non-proprietary alendronate. The guidance offers no analysis.	Section 4.2.11 of the FAD explains the Committee's decision to exclude the modelling of breast cancer benefits for raloxifene in the cost effectiveness analysis.
	i) whether you consider that all of the relevant evidence has been taken into account; It is now well over 4 years since the last formal submissions of data from the original stakeholders, including manufacturers other than strontium. Additional information on fracture risk has been incorporated, but Lilly no longer remains confident that all relevant evidence has been taken into account. Particularly for severe osteoporosis, the current cost effective model could be seriously underestimating the value of preventing further fractures, in patients with an inadequate clinical outcome from antiresorptive drugs. Lilly is aware of the following data that almost certainly has not been incorporated in the Assessment group's model: **Further Data** Important data from a UK study has been published by Arden et al (2006) which shows that persistence with teriparatide at 1 year is very high (87%) and probably greater than that of other therapies for osteoporosis. Recent unpublished follow-up data from the study shows that 79% of patients completed the full 18 month course (data on file: analysis of initial 1,107 patients). The high persistence rates should help to optimise the effectiveness of teriparatide in patients who are high risk.	Although unusual to consider late evidence, the Committee was aware of the time elapsed since the manufacturer's submissions for this appraisal and therefore noted the data contained in the manufacturer's comments at various stages of consultation. The Committee concluded that the data provided would not change their recommendations for teriparatide for the initiation of secondary prevention treatment.

Consultee or Commentator	Comment	Institute Response
	The Observational Study of Severe Osteoporosis (OSSO) is the first prospective study designed to understand the impact of an inadequate clinical outcome to osteoporosis drug therapy. The primary objective is to evaluate changes in health-related quality of life in postmenopausal women with osteoporosis who have an inadequate response to anti-resorptive medications. Baseline data have been published by Jakob et al (2006) and 12 months (final) data have been presented at ECCEO and ASBMR. [In confidence data included in the comment removed] • Using a simple definition of inadequate clinical outcome the study recruited a severe population (N=2322, mean age 70.2, mean lumbar BMD T score -3.1) and low mean utility based on EQ5D (0.47 and 0.53 for women enrolled because of fracture while on antiresorptive or intolerance to antiresorptive respectively.) • The subsequent fracture rate was high: 8.8% of women reported clinical fractures in 12m. • Women with a fracture in the 12 months prior to study baseline were significantly more likely to sustain an incident fracture during follow-up than those without prior fracture (hazard ratio 1.92; 95% CI: 1.38, 2.68; p<0.001) • There were large swings in utility according to fracture status at baseline and incident fracture status • The pattern of recovery and decline in HRQoL shows a population with a systematically lower utility than predicted in the Assessment Group cost-effectiveness model. The utility multipliers in the model, would have women aged 70 to 79 years moving from 0.74 to 0.62 (a range of 0.12) and then to 0.69, as they fracture and recover. In OSSO, even women with no fracture for 24 months (12 months each pre- and post- baseline) had a mean HSV value lower than those in this range; the women, on average, moved between 0.62 and 0.37 (a range of 0.25). Therefore the model underestimates the impact of repeated fractures in reducing HRQoL to persistently low values and underestimates the impact of a further fracture in this population. Overall, this has the effect of underestimating the value of treatments shown to reduce the risk of fracture. • Although not planned, during follow up 348 patients started teriparatide treatment. Patients in Germany – with early access - were most likely to start teriparatide. Patients starting teriparatide had fewer incident fractures compared to those who did not (1.7% vs. 10.2%) but no statistical comparison has been performed of fracture rates, due to the variation in time from baseline to teriparatide start (77% within 3 months of baseline) and possibility that confounding factors were not measured in the study.	Although unusual to consider late evidence, the Committee was aware of the time elapsed since the manufacturer's submissions for this appraisal and therefore noted the data contained in the manufacturer's comments at various stages of consultation. The Committee concluded that the data provided would not change their recommendations for teriparatide for the initiation of secondary prevention treatment.

Consultee or Commentator	Comment	Institute Response
	[In confidence data included in the comment removed] **The European Forsteo® Observational Study (EFOS)** is a pan-European 3-year, prospective observational program designed to evaluate the long-term effectiveness of teriparatide in a naturalistic setting. The primary objective is to determine the incidence of clinical vertebral and nonvertebral fragility fractures in postmenopausal women treated with teriparatide for a maximum of 18 months, with a post-treatment follow-up of up to 18 months duration. Secondary objectives include the determination of the occurrence of back pain, effects on health-related quality of life, treatment compliance, and fracture-associated treatment direct costs. (Baseline posters have been presented at ASBMR 2006, EULAR 2006 and ACR 2006). [In confidence data included in the comment removed] • The study enrolled 1645 teriparatide patients (mean age 71.5, mean lumbar BMD T score -3.3, mean prior fractures 2.9) • Mean HSV score from EQ5D was 0.41 • Using EQ5D 31% of patients reported extreme problems in Pain/Discomfort and 15% reported extreme problems in Usual Activities. • The patients enrolled in this study showed more severe osteoporosis than in OSSO and had lower quality of life. The ongoing follow up will reveal their subsequent outcomes compared to OSSO patients. • An analysis of Swedish patients for the Pharmaceutical Benefits Board showed that >90% met the reimbursement criteria agreed, and the patients were more severe than the total study population. This shows that physicians in Sweden were prescribing teriparatide appropriately. [In confidence data included in the comment removed] Therefore, further evidence should be taken into consideration regarding the following factors: • Persistence with teriparatide is very high with a high majority completing the full 18 month course • Women with fractures have lower HRQoL (utility) that has been assumed in the economic model. Therefore the model underestimates the impact of repeated fractures and thus the value of treatments shown to reduce the risk of fracture. • [In confidence data included in the comment removed]	Although unusual to consider late evidence, the Committee was aware of the time elapsed since the manufacturer's submissions for this appraisal and therefore noted the data contained in the manufacturer's comments at various stages of consultation. The Committee concluded that the data provided would not change their recommendations for teriparatide for the initiation of secondary prevention treatment.

Consultee or Commentator	Comment		Institute Response
	[References given]		
Nycomed UK Ltd.	We write to express our concerns regarding the preliminary recommendation pertaining to the NICE issues Appraisal Consultation Document on secondary prevention osteoporotic fragility fractures in post menopausal women. Although we were ineligible to register as a stakeholder at the time, we have subsequently launched PTH(1-84), an anabolic agent for the treatment of post menopausal women with osteoporosis at high risk of fracture, and thus currently have a major commercial interest in this area. The preliminary recommendation is for the initiation of alendronate for secondary prevention in osteoporosis in high risk post menopausal women. However, the guidance specifically excludes those women who, for whatever reason, have to be withdrawn from initial therapy. We know that some 20% of patients will be intolerant to alendronate and that up to fifty percent will discontinue in the first year of treatment. Thus, there is a significant and important population of patients that are in effect are now being excluded. Previous NICE guidance has advised on the use of alternative treatments including the PTH product teriparatide and hence funding provision in the UK is currently available, albeit generally poor with regional variability and inequality of access. Funding is especially poor compared with other European health systems where anabolic agents are widely prescribed. The proposed recommendation does little to improve this situation and is likely to exacerbate it, with payers, in the absence of specific guidance, able to restrict or withdraw funding for alternative treatments so further disadvantaging this population. We therefore feel that the recommendation should specifically address the provision of funding for the identified population. We suggest that a statement to the effect that pending the publication of clinical guidelines (in preparation) in patients who are either intolerant or unresponsive to alendronate, alternative treatments should be funded based on individual clinical need. Thank you for your consideration of this matter. [Electronic version requested]		Comment noted. Comment noted. The clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' will include guidance on treatment options for those who have withdrawn from initial treatment. Comment noted. Funding decisions of PCTs are not the responsibility of the Institute.
Professional and Patient Groups			
British Geriatrics Society - Falls and Bone Health Section	–	This response replaces my previous response (submitted on Friday 23 March) in the light of revisions from other executive members of the British Geriatrics Society Falls and Bone Health Section. This response may now be considered the official view of the BGS Falls and Bone Health Section. Time has not permitted full discussion with the BGS UK Management Committee as a whole; hence the response may only be taken as representing the Falls and Bone Health sub-group.	Comment noted.

Consultee or Commentator	Comment		Institute Response
	1	The removal of an absolute requirement for DXA scanning in older women is welcomed, and reflects the pragmatic approach that is often appropriate in older, frailer women. We suggest the following addition to this section: Most non-vertebral fragility fractures occur after a fall. Falls prevention is therefore an important component of a clinical strategy to prevent fractures. For older people, this guidance should be read and applied in the context of an integrated approach to falls and fractures as indicated in NICE Guidance CG21. We recognise that this guidance concerns initiation of therapy for secondary prevention. In the absence of any consideration of second line therapy, we suggest that the guidance makes explicit reference to the need to refer to the forthcoming guideline (Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk) for patients who withdraw from initial treatment, for whom the recommended treatment is unsuitable or for whom there is evidence of inadequate response to this treatment. Publication of this forthcoming guidance is urgent. Until then, patients should not be denied second line treatments.	Comment noted. The clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' will include guidance on second line therapies.
	4	The evidence and interpretation is complex, particularly with regard to cost effectiveness modelling. The primary recommendation of Alendronate for first line therapy is reasonable and consistent with current evidence and costs. It is sensible that the previous recommendation of etidronate (in the last version of this ACD) has been removed, as the evidence is of lower quality. NICE"s own cost effectiveness models do not demonstrate a lack of cost-effectives for Risedronate, Etidronate, Strontium or Teriparatide in older women. The text implies that all 4 drugs have ICERs below the 30,000/QALY threshold in women over 70. The logic of recommending alendronate ahead of other drugs in the same class makes sense, due to the lower cost and greater cost effectiveness. But it is urgent that the other treatment options are included in the forthcoming clinical guideline. The comments regarding calcium and vitamin D are consistent with current evidence. The specific comment regarding the high incidence of deficiency states in older women is welcomed.	Comments noted.
	6	These recommendations are welcomed. Section 4.1.11 also implies a need for further research into the efficacy of teriparatide and the identification of subgroups that may benefit from this agent. This should be made as a formal recommendation in this Section.	Comment noted.
	8	The guidance will need to be reviewed sooner if there is a significant reduction in cost of any of the drugs in this ACD. Alternatively, the recommendations may suggest a cost threshold, below which each of the other drugs might be considered to have sufficiently favourable ICERs.	Technology appraisal guidance is reviewed when new evidence becomes available, this includes in this case the publication of the

Consultee or Commentator	Comment		Institute Response
			WHO algorithm. Consultees can request an early review if significant new data become available.

Reply received but no comments:

- NONE

Comments received from website consultation:

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
Patient 1	2	Osteopenia: T-score of between -1 and -2.5 SD. Is not correct. My T-Score is above this but following a bone biopsy severe osteopenia was diagnosed along with adynamic cells	The osteoporotic range is internationally recognised as a T-score of between -1 and -2.5 SD
	4	Having had a hysterectomy age 40 in 1995 I was unable to have any HRT after a calcaneal fracture in 1997 Diagnosis of Membranous Glomerulo-Nephropathy at 45 followed by pulmonary embolism in 2000 I was diagnosed with Osteopenia in 1994 following Rx with Calcium and in 2000 I stopped. In 2002 following a fracture started alendronate. 2004 I had 2 fractures and stopped the alendronate and started Calcitriol. My Consultant requested Teriparatide but it was refused as my T-score was within normal limits. I sent many letters requesting that this was looked at in Nov I was asked to have a second opinion, calcitriol increased, pamidrimate infusion with side effects I didn"t like, refused any more. Fracture vertebra, Vertebroplasty requested by me didn"t happen. Dec 2004 requested a bone biopsy, done in April 2005, result June 2005 Adynamic bone, severe osteopenia. Only treatment Teriparatide. Feb 2006 new vertebral fracture for vertebroplasty, old fracture unable to be done. Teriparatide Finished in Feb 2007 2 Fractures on xray and 2 days ago bad cough broke rib. Wish I had been able to start treatment sooner. For repeat bone biopsy soon. I feel very let down by the system	Comment noted.
	6	Would it be possible for someone to Research: following cessation of the contraceptive pill that there is not a decrease in turnover of bone cell activity and that decrease starts at an earlier age than previously thought, and this in conjunction with the ever increasing weight and height of the population? And Secondly the factor that when people have Polycystic ovarian disease that at present there is no proof of the turnover of bone cell activity when the Follicle Stimulating Hormone and Luteinising Hormone are not within the correct ratio and periods are not regular, T-scores may be within normal limits but are they accurate?	This is outside the remit of the current appraisal. This may be considered in the clinical guideline on ‘Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk’.
	7	The original guidance on Teriparatide didn"t work for me. This needs to be looked at again.	Comment noted.
Patient 2	–	male sufferer, family history, 4 x spinal fractures, age - under 60 yrs old	Comment noted.
	1	Drug treatment(including those in 1.2 if appropriate) should be made available to all post menopausal women who are at high risk of breaking a bone regardless of age or previous fracture. Any resulting fracture after menopause is likely to cause extreme pain and loss of quality of life leading into painful old age. Preventative medication also	Comments noted. The secondary prevention FAD contains recommendations for all post-menopausal women with a T-

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
		reduces future costs to the NHS.	score of -2.5 SD or below who have suffered an osteoporotic fragility fracture.
	2	The incidence of osteoporosis in men should not be down graded(2.2)on the basis of accelerated bone loss in women. Men suffer from osteoporosis - their needs should be considered equaly. Clearer guidance is needed on the treatment of men. The same symptoms occur and are equaly painful and life changing.	The clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' will include guidance on treatment options for men.
Public 3	1–8	Drug treatments should be available for all post-menopausal women who are at high risk of breaking a bone, regardless of their age, even if they have not broken a bone.	Comments noted. The secondary prevention FAD contains recommendations for all post-menopausal women with a T-score of -2.5 SD or below who have suffered an osteoporotic fragility fracture.
Public 4	–	My elderly Mother has had osteoporosis for several years, and has been treated on Alendronate until recently. Despite treatment she has had further height loss and back pain and last year it was discovered that she had had several new fractures of the spine. Her spine had weakened since her last visit to the consultant and it was suggested she try a new treatment called Forsteo. After a long delay (we were told it was due to funding) she started the treatment in October. At her 6 month check up she had improved tremendously. She can now stand up without pain, she has had no further fractures and is generally enjoying her life more. I am astonished that no guidance is given in this document for those patients who do not respond to the first and cheapest available treatment. These are the most vunerable people and suffering with the severest degree of osteoporosis. I am told by my mothers consultant that should this document be ratified that funding will no longer be available and I strongly object.	Comments noted. The clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' will include guidance for those who do not respond to the initiated therapy.
NHS Professional 1	1	This is much better as it leaves the clinical decision making guidance that will inform the use of second line therapies or any treatment in high risk osteopenic women to the GDG. A simple additional statement would be wise acknowledging the data sheet contra-indications (oesophageal abnormalities, stricture, achalasia or inability to remain upright for 30 minutes) otherwise the guidance could be criticised for encouraging unsafe prescribing practice in the small number of women for whom alendronate would be contra-indicated	Comment noted. Clinicians should be aware of any possible contra-indications before prescribing treatments or refer to the Summary of Product Characteristics (SPC).

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NHS Professional 2	–	These guidelines should give clinicians the right to use other agents in those intolerant of alendronate	Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
	1	Clinicians should be able to prescribe other drugs for those patients who cannot tolerate alendronate	Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
NHS Professional 3	1	This is of limited use. Like other groups of drugs, not all women will tolerate alendronate; why not suggest at least 1 alternative as in TAG87? Primary Care teams will be left floundering. Osteopaenia is associated with increased fracture risk and a minority of fractures occur in women with T score below -2.5; with falling cost of alendronate, why not lower the threshold to treat and reduce fractures? Remember, -2.5 is an artificial threshold and other guidelines (eg USA) use different levels for both idiopathic and steroid related "porosis to allow more people to be treated. Why not omit etidronate altogether? The quality of data is very poor. If etidronate is in, why not clodronate?	Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
	2	Fine; emphasises the need to tackle the problem and give comprehensive guidance, not just "generic alendronate"	Comment noted.
	3	Fine, but why not then suggest an order of use as in TAG87?	Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in

Consultee or Commentator	Section of ACD (if specified) - Comment		Institute Response
			individuals at high risk'.
	4	Why has the model changed from TAG87? With lower price, it should be possible to treat more women with alendronate eg those with Tscore -1 to -2.5 Persistence is better still with monthly ibandronate, but it is not mentioned Teriparatide does not work as well after alendronate; several studies confirm. So, why use it later, when bones loaded with a bisphosphonate and it"s of little help? Remember, teriparatide studies were in bisphosphonate-nieve patients and not in pts with bones holding long-acting alendronate. Why not use it first in those with v low BMD and say 2 fracures and maintain bone gained with alendronate? Why no mention of i.v. bisphosphaontes for pts not able to tolerate oral or those with malabsorption eg Crohn"s or coeliac disease?	In the FAD all postmenopausal women with a fracture and a T-score of -2.5 SD or below can receive treatment for the secondary prevention of osteoporosis. This is more permissive than the recommendations in TA 87.
	5	Difficult; in effect, any teaching to GP"s is to use alendronate and you give no guidance thereafter! This makes the TAG of limited use as all groups of drugs (statins, ACE inhibitors etc etc) are switched from one to another if the first causes side effects or is ineffective; guidance on a second or third agent for osteoporosis would be welcome here (what might be produsedby the Guideline Group is not binding on hospital or NHS Trusts whereas this TAG is)	Comments noted. The clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' will include recommendations for women contra-indicated or withdrawing from the initial therapy. The Healthcare Commissions monitors the implementation of both technology appraisals and clinical guidelines.
	6	6.1 repeats what doctors have said for years but has no clout. Who will fund such massive studies, which need to look at fractures and not just BMD? 6.4 misses the point as strontium DOES interfere with dexa results for years after treatment. Nomograms to allow for this have been published	Comment noted.
	7	7.1 and 7.2 are weakened by the empasis on generic alendronate with no alternative even if contraindicated or ADR"s develop Teriparatide will only show the benefit demonstrated in trails (eg Neer et al NEJM) if use in bisphosphonate nieve pts and you should say so	Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
	8	Too late. There is already data on monthly oral ibandronate and i.v. bisphosphonates	Ibandronate and PTH 1-84 have

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		not considered here and another PTH preparation (1-84 PTH); "suggest July 2009 Has advice from the experts, who actually treat osteoporosis, been heeded? The Committee seems under-represented in this regard	not yet been referred to the Institute for Appraisal. Technology appraisal guidance is reviewed when new evidence becomes available, this includes in this case the publication of the WHO algorithm. Consultees can request an early review if significant new data become available.
NHS Professional 4	1	We need options for those in whom alendronate is unwise or are intolerant of alendronate. Should this be published at the same time as Clinical Guidance, rather than piecemeal. What happens when patients ""fail"" whilst taking alendronate. Do we revert to TA 87?	The technology appraisal should be read in conjunction with the clinical guideline when it is published.
	2	?smoking, liver disease, traeted bone disease, drugs eg aromatase inhibitors This needs to be taken as a whole with clinical guidelines	Comment noted.
	5	We need to advise those for whom alendronate is contraindicated or intolerant of the drug. TA 87 still guides us for those who ""fail"" whilst taking alendronate	Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
NHS Professional 5	–	I have been asked to respond to this ACD on behalf of the British Geriatrics Society.	Comment noted.
	1	The primary recommendation of Alendronate for first line therapy is reasonable and consistent with current evidence and costs. The removal of an absolute requirement for DXA scanning in older women is welcomed, and reflects the pragmatic approach that is often more appropriate in older and frailer women. However, the lack of any consideration of second line therapy is disappointing. The evidence from the cost effectiveness modelling, commissioned by NICE, clearly indicates that other agents are also cost effective (using the ICER threshold of 30,000 per QALY), particularly in older women, who have the highest fracture risk. It is illogical for NICE to provide no guidance on second-line agents. If Alendronate is not tolerated, then other agents that are within the cost-effectiveness threshold should be recommended for second-line use. As it is	Comment noted. The clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' will include guidance for those who do not respond to the initiated therapy.

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		likely that the main reason for needing a second line agent will be adverse effects, the second line agent should not be another bisphosphonate.	
	4	The evidence and interpretation is complex, particularly with regard to cost effectiveness modelling. It is sensible that the previous recommendation of etidronate (in the last version of this ACD) has been removed, as the evidence is of lower quality. NICE"s own cost effectiveness models do not demonstrate a lack of cost-effectiveness for Risedronate, Etidronate, Strontium or Teriparatide in older women. The text implies that all 4 drugs have ICERs below the 30,000/QALY threshold in women over 70. The logic of recommending alendronate ahead of other drugs in the same class makes sense, due to the lower cost and greater cost effectiveness. But it is not logical to disregard non-bisphosphonates on the same grounds and clinicians will require advice on the most appropriate second-line therapy. Strontium appears to be the most cost effective drug for the very large number (10-84%) of women that will discontinue a bisphosphonate but still require effective treatment of osteoporosis. The comment regarding calcium and vitamin D are consistent with current evidence. The specific comments regarding the high incidence of deficiency states in older women is welcomed	Treatment options for women who are contra-indicated to alendronate and for second line options will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.
	6	These recommendations are welcomed. Section 4.1.11 also implies a need for further research into the efficacy of teriparatide and the identification of subgroups that may benefit from this agent. This should be made as a formal recommendation in this Section.	Comment noted.
	8	The guidance will need to be reviewed sooner if there is a significant reduction in cost of any of the drugs in this ACD. Alternatively, the recommendations may suggest a cost threshold, below which each of the other drugs might be considered to have sufficiently favourable ICERs.	Technology appraisal guidance is reviewed when new evidence becomes available, this includes in this case the publication of the WHO algorithm. Consultees can request an early review if significant new data become available.
NHS Professional 6	–	I am a clinician running a Falls and Osteoporosis Clinic. I am the DoH Medical Library of Health expert for Orthogeriatrics	Comment noted.
	1	I have no problem with starting most patients on generic alendronate (but see my comments below)on grounds of cost effectiveness. BMD alone however is not the only predictor of further fracture eg family #, low BMI,frequent falls - withholding treatment from a patient who has fractured with other risk factors but whose T score is eg -2.4 is illogical - experienced clinical judgement must be allowed.	Comment noted.

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	2	No mention is made of falls prevention-the whole point of the exercise is to prevent fractures and to advise treating secondary osteoporosis with drugs alone without including a reference to falls prevention will not meet the aim of the exercise ie to reduce the re-fracture rate I don"t understand the last couple of lines of 2.11-by definition secondary prevention (to which this guidance addresses itself)requires a prior fracture. In the light of the importance these guidelines give to BMD measurement, insufficient detail has been to the interpretation of lumbar spine T scores. These are often problematic in the older patient as degenerative changes may give a falsely high value and it is not uncommon to find the lumbar spine osteoporotic while the hip is not. In these cases forearm measurements are necessary but these are often not routinely measured	Comment noted.
	4	Consideration needs to be given to the group of patients, usually but not exclusively elderly, who have difficulty self-administering their drugs. Although the guidance considers compliance and persistance, few compliance studies appear to have included correct administration (empty stomach, 1/2hr wait before food etc). On account of the problems with bisphosphonate administration those patients, who may be demented ,who require a care assistant to give them medication will often not receive a carer first thing in the morning and therefore will not be able to comply. In addition for those who require a carer to get them up and give them breakfast, it is very unusual for the care assistant to have time to get the patient up, administer the alendronate and then wait at least 1/2 hour before giving them their breakfast and the rest of their medication. Equally in care homes,especially residential homes, anecdotally I suspect that few will do a special drug round and the alendronate is being given on the drug round with the other drugs. In these elderly patients strontium may be more effective to administer especially if they have a carer to put them to bed or on the night drug round.	Comment noted. The clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' will include guidance on persistence and compliance to drug treatments.
	6	Administration of bisphosphonates in a care home setting-are the administration precautions complied with?	Comment noted.
NHS Professional 7	–	I am on a Servier nursese focus group and I have given talks for other companies. The monies received were given to charities.	Comment noted.
	1	The only data we have for older women (80+) are for Risedronate (spine) and Strontium (spine & hip). Why can"t they be front line treatment? especially for older people who have difficulty swallowing due to severe kyphosis or for people who find it difficult to swallow a pill with a huge glass of water, especially early in the morning.	Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'

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	4	As i have mentionned in my comments in the primary prevention, Etidronate is NOT well tolerated and is not licensed for oP at the hip.Why do you keep on about putting it on the same line as Alendronic Acid and Risedronate?	Etidronate (Didronel PMO) is licensed for the treatment of osteoporosis, and prevention of bone loss in postmenopausal women considered at risk of developing osteoporosis.
	5	OP treatments are long-term and compliance is poor it is therefore crucial that there should be some possibility of patients" choice in deciding which medication suits their condition best. In the long-term it must surely be cheaper to prevent a fracture by taking a more expensive medication than having a repeat fracture because the medication did not suit the patient and therefore stopped taking it.	Comment noted. The clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' will include guidance on persistence and compliance to drug treatments.
NHS Professional 8	1	It is fair enough to use alendronate as first line in fit patients and good to see cut off now fits clinical practice. However I would not be happy to have to use alendronate in patients with pre existing gastic problems or indigestion. Clinicians should have freedom to choose other treatment first if there are reasons Alendronate may exacerbate a pre existing condition. Teriparatide is an important treatment for severe osteoporosis. Please keep old recommendation on this. Failure to recommend in technology appraisal means we will effectively loose funding for it, and hence loose this treatment. A guideline recommendation is not enough.	Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' Teriparatide is not recommended as a treatment option for the initiation of secondary prevention of osteoporosis.
	4	Cutting recommendations to just initiation of therapy is un helpful for physicians. We still need permission in the technology appraisal to use teriparatide second line in severe cases, as per current guidance.	Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' Teriparatide is not recommended as a treatment option for the initiation secondary prevention of osteoporosis.

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NHS Professional 9	–	Lead clinician in osteoporosis (North Durham) Medical Adviser to Durham branch of the NOS Support Group Member Regional Advisory Board for Osteoporosis	Comment noted.
	1	1.1 , 1.2 Recommend add ""unless contraindicated (eg oesophageal dysmotility, creatinie clearance <30mls /min etc)when alternatives may be considered"". There is in addition some evidence for more rapid onset of action of other bisphosphonates, which may be important in initiating therapy and reducing incidence of further fractures. This wording may have the effect of patients not being treated at all if alendronate is contraindicated.	Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'
	2	2.11 and 2.12 Historically all guidelines have taken excess alcohol to be as the current guidelines (>14 units per week for women) and low BMI to be <19; there is no reference in this document as to why these have been changed.	2.11 and 2.12 refer to clinical risk factors for increased risk of fracture in risk of low BMD.
	4	I am still concerned that this will be taken to read that unless alendronate is tolerated no other therapy will be ""allowed"" by NICE; in reality, this is presumably not the intention, but until the clincal guidelines are published this may be the effect of this document read in isolation. A woman therefore presenting with her first clinical fracture may not be treated if unable for whatever reason to take alendronate.	Treatment options for women who are contra-indicated to alendronate will be defined in the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'
	5	5.3 This should be available in conjunction with this appraisal, or at least an idea should be given as to when it is expected for the reasons given above.	Comment noted.
	6	6.4 Providing the therapy and duration is documented, a correction can be applied if DXA scanning is clinically indicated after strontium treatment.	Comment noted.
	8	8.2 Already there are new bisphosphonates available which have not been covered by this appraisal. A review date 3 years hence may be too long, as some are already in use and others expected to be shortly. As oral intolerance is the main reason for cessation of bisphosphonate therapy, parenteral preparations are of particular interest.	Technology appraisal guidance is reviewed when new evidence becomes available, this includes in this case the publication of the WHO algorithm. Consultees can request an early review if significant new data become available.
Other 1	–	I have served as a consultant and received honoraria and travel expenses from MSD-Asia and Roche Products UK. I have also attended a national meeting sponsored by Servier and a regional symposia sponsored by Nycomed. Until October 2005, I was an employee of Merck, Sharp and Dohme UK Limited. Since that date, in addition to	Comment noted.

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		independent consultancy activities, I have been employed as a part-time lecturer at the University of Derby and devote charitable time to the International Society for Fracture Repair"s Osteoporotic Fracture Campaign. The views expressed here are my own and are not intended to represent the views of either the University of Derby or the ISFR.	
	1	Poor persistence with bisphosphonates is well documented (Osteoporosis Int 2007 ""A systematic review of persistence and compliance with bisphosphonates for osteoporosis"" Cramer JA et al). The literature would suggest ~50% persistence at 1 year post-initiation the reasons for which are multi-factorial. Accordingly, implementation of this TA will result in a substantial absolute number of patients requiring access to a 2nd line agent. The non-mandatory nature of Clinical Guidelines could undermine care for patients that withdraw from alendronate treatment. 2nd line agents should be explicitly endorsed by this TA in priority order.	Comment noted. The clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' will include guidance on second line therapies. The Healthcare Commissions monitors the implementation of both technology appraisals and clinical guidelines.
	4	NICE Technology Appraisal 87 placed teriparatide as a 2nd line agent to bisphosphonates. This product positioning is curious in light of findings from a study of another PTH agent (PTH 1-84: NEJM 2003;349:13:1207-1215, editorial on this at NEJM 2003;349:13;1277-1279). The so-called PaTH Study suggested a blunting effect of PTH therapy amongst patients pre-treated with alendronate. Accordingly, TA87 appears to have placed teriparatide, albeit pragmatically, in a sub-population of very high fracture risk patients that are potentially unlikely to experience an optimal response to the most expensive drug available. Would the evidence not suggest that if PTH analogues are to be endorsed by NICE TA and/or CG at all, that this should be in a bisphosphonate naive patient with a history of multiple fractures, the number of fractures being determined by budgetary implications (at least 2, but probably 3), and therefore be a 1st line agent for a small sub-population of very frail, very high fracture risk patients that experience recurrent fractures? Not to position PTH in this fashion may result in NICE endorsement of an illogical treatment paradigm as is the case currently for TA87.	Teriparatide is not recommended as a treatment option for the initiation of secondary prevention of osteoporosis.
	5	Integrated models of care referred to as ""Fracture Liaison Services"" have been developed across ~30% of the UK hospital sector to effectively implement secondary prevention of fracture strategies as outlined in Technology Appraisal 87 (Osteoporosis Int 2003;14:1028-1034 and Best Prac Res Clin Rheum 2005;19:6:1081-1094). The FLS concept has been recognised nationally (DOH - Musculoskeletal Services Framework p33 and BOA - Blue Book 2003 on care of the fragility fracture patient) and internationally (JBJS 2004;86B:958-961 and J Am Acad Orthop Surg 2004;12:385-395) as a means to ensure osteoporosis assessment for every fragility fracture patient >50	Comment noted.

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		years presenting to hospital. FLS is a proven model of healthcare delivery that can achieve rapid national implementation of this technology appraisal for patients with new fractures if adequately resourced.	
	6	A national research network comprised of hospitals with effective Fracture Liaison Services (Osteoporosis Int 2003;14:1028-1034 and Best Prac Res Clin Rheum 2005;19:6:1081-1094) would provide a means to recruit patients to large scale observational active comparator studies for current therapies and agents to be licensed in the future. Generic alendronate could serve as an active comparator for such studies to explore clinical and health economic benefits of new agents, particularly anabolic therapies. Five year studies randomising fragility fracture patients to 12/18/24 months treatment with anabolic agents to be followed by 48/42/36 months alendronate therapy versus an active comparator group of 60 months alendronate therapy, stratified by absolute fracture risk profile, would serve to demonstrate which sub-populations, if any, of fracture patients might benefit from costly anabolic treatments.	Comment noted.
	8	Several new technologies are likely to be licensed during the proposed timeframe including an annual i.v bisphosphonate which may offer significant improvements in tolerability, compliance and persistence. An annual administered bisphosphonate will present a challenge to health economic modelling; the likely benefits of improved compliance may off-set differential acquisition cost relative to generic alendronate. Single technology appraisals for this agent and new anabolic therapies may be required during the period 2007-2010 in order to ensure timely access to therapeutic innovation, if demonstrated to be pharmaco-economically desirable, for UK patients relative to the dates for approval of marketing licenses.	Technology appraisal guidance is reviewed when new evidence becomes available, this includes in this case the publication of the WHO algorithm. Consultees can request an early review if significant new data become available.