NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

Health Technology Appraisal

Strontium ranelate for the prevention of postmenopausal osteoporotic fractures

Response to consultee and commentator comments on the draft scope

Consultee	Subject in Scope	Comment	Response
National Osteoporosis Society / supported by ARMA		The NOS is satisfied that the draft scope re strontium ranelate identifies the correct population, comparators and outcome measures for the technology appraisal to be completed appropriately.	
	Background	On a minor point, we would like to suggest that the final sentence of the fourth paragraph describing the background to the technology is re-worded to acknowledge that HRT is no longer considered a first line treatment for osteoporosis.	The scope has been amended to include a footnote stating the CSM advice.
MSD	Objective / remit	As indicated to the the DoH during the 10th wave consultation, MSD is of the view that it is not a valuable use of NICE's resources to refer yet another Osteoporosis HTA to the Institute, separate to the existing framework of (forthcoming) assessment and guidance. Etcetera.	
		For clarity the, 'prevention' should be defined as primary and/or secondary prevention of osteoporotic fractures as appropriate.	The scope comprises both primary and secondary prevention of osteoporotic fractures.
	Population(s)	The patient population indicated in this appraisal differs from that of the existing Osteoporosis appraisals / guidance. This will be confusing for patients and clinicians alike and we urge NICE for consistency. Additionally, there is not currently a reliable method of quantifying all clinical risk factors. Work to assess the contribution of risk factors to the development of osteoporotic fractures is ongoing and will not be available by the closing date for submissions in January 2006. This is	Interventions in the clinical management of osteoporosis are used to prevent an initial osteoporotic fracture (primary), and/or to prevent subsequent fractures (secondary) where a

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		a fundamental weakness of this Technology Appraisal.	fracture has already been sustained. The title, objective and population described in the current scope cover these aims of clinical management.
	Current standard treatment (comparators)	It is neither ethical nor reflective of current clinical practice to compare strontium ranelate to 'no treatment'. Given the conclusions of the NHSC that 'it is unclear at this stage what the place of strontium ranelate in the prevention and management of osteoporosis will be, in particular its relationship with bisphosphonates and HRT, MSD is of the view that further clinical research is required so as to allow patients and prescribers to determine its position with respect to other, well established, technologies.	The wording in the section of the scope that relates to current standard treatment (comparators) has been amended to cover all possible comparisons.
	Outcomes	MSD is very concerned to see that long-term outcomes such as monitoring of fracture reduction have not been identified for consideration. MSD would additionally highlight the difficulty of demonstrating the confounding effect of strontium ranelate on BMD [NEJM 2004; 350: 5 January]. Most importantly however, the lack of 5 year data on strontium ranelate will pose challenges in economic evaluation.	Outcomes include fractures.
WAG	Background	In the background information it states that " an estimated 1.2 million women have osteoporosis in England and Wales" In the NICE Appraisal Consultation Document : Technologies for the prevention and treatment of osteoporosis and prevention of osteoporotic fractures in postmenopausal women, it states in paragraph 2.5 that " it is estimated that there are 2.1 million women with osteoporosis in England and Wales". Both documents appear to be using the same WHO definition of osteoporosis.	The FAD for Secondary prevention states that 'It has frequently been quoted that over 2 million women have osteoporosis (that is, have a T-score below –2.5 SD) in England and Wales. However, recent epidemiological data based on a UK sample indicate that this figure may be closer to 1.2 million' [July 2004, page 4].

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	Population	In the population to be studied, it does not mention the criteria for ' being at risk of osteoporotic fractures' .Presumably they will be as in the aforementioned document of - smoking, low body mass index, early menopause, family history of osteoporosis, long term systemic corticosteroids and conditions affecting bone metabolism.	Evidence on specific risk factors (appropriateness and magnitude of influence) is constantly emerging. New insights will be incorporated in the appraisal.
BSR / supported by ARMA	None – planning of project.	The main concern with the current draft scope is that it focuses on the prevention of postmenopausal osteoporotic fracture, while blinding itself to progress in osteoporosis as a whole by the National Institute for Clinical Excellence. The most recent technology appraisal on osteoporosis separates out the clinical effectiveness and cost-effectiveness of technologies in the secondary prevention of osteoporotic fracture in postmenopausal women (and considers raloxifene, alendronate, risedronate, and teriparatide in this context). The most streamlined approach to strontium would be to insert it into exactly the same cost utility analyses. Thereafter, there will be an appraisal on the clinical and cost-effectiveness of technologies for the primary prevention of osteoporotic fragility fractures in postmenopausal women. The models for this appraisal are being constructed at the present time and it would make most sense for strontium ranelate to be included with the other agents in this category also. Finally, it would be sensible for strontium ranelate to be included in the clinical guideline entitled *Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk*.	While it might appear an attractive option to combine the appraisal of strontium ranelate for the prevention of osteoporotic fractures in post-menopausal women with osteoporosis with the ongoing appraisal of primary prevention of osteoporotic fractures in postmenopausal women, several factors mitigate against this. Please see endnote for the full text that has been included in the cover letter to consultees and commentators to this appraisal.[i]
Society for endocrinology	None – planning of project	… although we would want to reinforce the importance of the guidance being conducted in accordance with the Institute's related osteoporosis guidance.	While it might appear an attractive option to combine the appraisal of strontium ranelate for the prevention of osteoporotic fractures in post-menopausal women with osteoporosis with the ongoing

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			appraisal of primary prevention of osteoporotic fractures in postmenopausal women, several factors mitigate against this. Please see endnote for the full text that has been included in the cover letter to consultees and commentators to this appraisal.[i]
Bone & Tooth Society / RCP	Background & Comparators	The World Health Organisation definitions for osteoporosis includes the term "established Osteoporosis" rather than "severe". The latter should be removed from the scope. Severity of disease is often based on clinical criteria. NICE have already tried to define this with regards to the use of teriparatide being restricted on the base of age, number of fractures, bone mineral density, and failure to respond to anti-resorptive therapy. It is important that there is consistency in the use of these terms. Calcitonin is not currently widely used in the UK for the management of patients with osteoporosis. This should therefore be removed as a comparator or standard treatment.	The scope has been amended following the suggestion by the consultee. Calcitonin is licensed for treatment of (established) post-menopausal osteoporosis and is as such a suitable comparator.
ScHARR	Current standard treatments (comparators)	In the section covering current standard treatments (comparators), where it says "if the evidence allows", we recommend that this be changed to "where published head-to-head RCTs of strontium ranelate and one or more of biphosphonates, SERMs and PTH exist, comment on the relative cost-effectiveness will be made."	The scope of this appraisal should cover all possible evidence that could be put forward to the Appraisal Committee. The scope should not exclude upfront the possibility to use indirect comparisons or direct comparisons based on non-

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	Outcomes Other considerations	In the outcomes section, we recommend that "adverse effects of treatment" be changed to "additional effects of treatment". These effects could be beneficial as seen in Raloxifene. We would be grateful for information regarding the anticipated license indications and price of the drug.	RCT evidence. The current wording in the scope sufficiently covers the possibility of considering 'additional effects of treatment'. The scope of an appraisal generally does not include the price of the intervention. The approved indication based on the positive opinion by the CHMP is included under 'technology' in the scope.
Novartis	Objective Outcomes	The objective states that it seeks "To establish clinical and cost effectiveness of strontium ranelate for the prevention of osteoporotic fractures in post-menopausal women". However, the CHMP indication for this product is one of treatment rather than prevention. It states that the approved indication is " Treatment of post-menopausal osteoporosis to reduce the risk of vertebral and hip fractures". This suggestion of prevention rather than treatment is continued by stating that strontium ranelate can be used "in post-menopausal women" when, in fact, it will only be those post-menopausal women who already have osteoporosis. In addition, if the indication for this product is restricted to vertebral and hip fractures, this should be acknowledged. We would suggest that the wording of the objective reflect the CHMP indication, such as: "To establish the clinical and cost-effectiveness of strontium ranelate for the treatment of post-menopausal osteoporosis in reducing the risk of vertebral and hip fractures" Outcomes to be considered are currently "Fractures (including hip, vertebra, wrist, proximal humerus)". However, in this context,	The scope has been amended to clearly state that post-menopausal women should have osteoporosis in order to be eligible for strontium ranelate. The scope has been amended following the suggestion by the

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		fractures are only relevant if osteoporotic in nature. Again, within the CHMP indication, the detailed fracture sites should be restricted to hip and vertebra. Therefore, we would suggest stating "Osteoporotic Fractures (including hip and vertebra)".	consultee.
Servier Laboratories	Objective Technology	As Protelos is the brand name in the United Kingdom and Osseor will not be used in this country, we request Protelos be given prominence This section does not refer to the class of drugs to which strontium belongs, namely, the DABAs. We request that this information be made available in the scope.	The scope has been amended following the suggestion by the consultee. The Institute is not aware of DABA being a recognised medical term nor was it used in the CHMP summary of opinion.
RCN	Population	it would be possible to confirm that there will also be some other NICE document that is addressing individuals with long term medical conditions who are at risk of osteoporosis related to their disease and or additional medications that will be considered for primary prevention? The above appraisal appears again to be specifying a specific group of postmenopausal women - this leaves out those with Long Term medical conditions (eg. rheumatoid arthritis, respiratory disease etc who may be inactive and below the postmenopausal or be male) who are at a high risk of osteoporosis.	The clinical guideline 'Osteoporosis' – see the scope on the Institute's website – will address patient groups with secondary causes. The intervention will be appraised according to its anticipated licence indication. The CHMP adopted a positive opinion on strontium ranelate recommending a marketing authorisation for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures.
P&G	Objective	The scope combines both the primary prevention and secondary prevention of fractures. Since the work performed by the DSU has not been completed, will the timings for the Strontium review allow for this?	While it might appear an attractive option to combine the appraisal of strontium ranelate

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	Current standard treatment (comparators)	Will the appraisal follow the development of the current osteoporosis appraisals, where primary prevention and secondary prevention are separated into two distinct Guidances? Please clarify is this is a full appraisal or an interim appraisal. What criteria and level of evidence needs to exist to determine if a comparator is appropriate?	for the prevention of osteoporotic fractures in post-menopausal women with osteoporosis with the ongoing appraisal of primary prevention of osteoporotic fractures in postmenopausal women, several factors mitigate against this. Please see endnote for the full text that has been included in the cover letter to consultees and commentators to this appraisal.[i] The Institute currently consults on a process for interim appraisals. This appraisal will follow the full appraisal process. A therapeutic intervention can be designated to be a comparator when it is licensed for use in the population to which the scope of the appraisal applies or when it is regarded as being standard treatment for this population.
Lilly	None – planning of project	Firstly, we would like to request that NICE ensure that the scope and method of appraisal in this case will be fair with respect to the current, ongoing Appraisal of drugs for Osteoporosis. In addition, we would also like to suggest that NICE take this opportunity to streamline the multiple related ongoing activities around osteoporosis. In view of the ongoing Technology Appraisal in this area, we wonder if, to avoid duplication of activity, the about-to-commence Primary	While it might appear an attractive option to combine the appraisal of strontium ranelate for the prevention of osteoporotic fractures in post-menopausal women with osteoporosis with the ongoing

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		Prevention Appraisal should be delayed to incorporate Strontium. Clearly it would not make sense to further delay the Secondary Prevention Appraisal which has been ongoing now for several years, and is reaching its conclusion. As Primary Prevention has not yet commenced it may be useful to include this Technology within it.	appraisal of primary prevention of osteoporotic fractures in postmenopausal women, several factors mitigate against this. Please see endnote for the full text that has been included in the cover letter to consultees and commentators to this appraisal.[i]
	Current standard treatment (comparators) Economic analysis Other considerations	We note that current standard treatment is 'no treatment (assuming adequate calcium intake and vitamin D replete'. We are puzzled by this, as clearly there are numerous alternatives in both primary and secondary prevention which NICE is currently reviewing. It is not clear how the economic analysis for the Appraisal of Strontium ranelate will tie in with the ongoing Osteoporosis Appraisal. It would seem important that targeting is clearly laid out, as is the case for the other therapies for osteoporosis.	The wording in the section of the scope that relates to current standard treatment (comparators) has been amended to cover all possible comparisons.

Statement of 'no comment':
North Sheffield PCT

[i] **Relationship with ongoing appraisals and clinical guideline**

As you are probably aware, this appraisal is taking place in the context of several related ongoing projects:

- An appeal is scheduled for October 2004 for the appraisal of bisphosphonates (alendronate, etidronate, risedronate), selective oestrogen receptor modulators (raloxifene) and parathyroid hormone (teriparatide) for the secondary prevention of osteoporotic fragility fractures in postmenopausal women;
- The appraisal of primary prevention of osteoporotic fractures in postmenopausal women is currently ongoing, and is anticipated to be published in September 2005;

- The clinical guideline osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk is anticipated to be issued in February 2006.

While it might appear an attractive option to combine the appraisal of strontium ranelate for the prevention of osteoporotic fractures in post-menopausal women with osteoporosis with the ongoing appraisal of primary prevention of osteoporotic fractures in postmenopausal women, several factors mitigate against this. Firstly, a new process has been published since the start of the primary prevention of osteoporosis appraisal, and it is not possible to combine two appraisals running to different processes. In addition, the appraisal of strontium ranelate covers both primary and secondary prevention aspects, whilst the appraisal of the bisphosphonates, selective oestrogen receptor modulators and parathyroid hormone has already been divided into two appraisals. Finally, it is anticipated that the guideline development group will use the economic model developed for the primary prevention appraisal. Combination of the two appraisals would lead to a delay, which would impact the guideline in addition to the primary prevention appraisal.

A representative of the osteoporosis guideline development group will be invited to attend each committee meeting on osteoporosis, and in turn the technical lead for the appraisal will be invited to attend each guideline development group meeting, to ensure a strong linkage between the development of the appraisals and guideline.

The Institute recognises the importance of maintaining a consistent approach towards the development of multiple pieces of guidance in a similar topic area. Therefore the School of Health and Related Research Assessment Group (ScHARR) will be carrying out the analysis for both the strontium ranelate and primary prevention appraisals, and the same economic model will be used for both appraisals. In addition, the same appraisal committee will consider both appraisals.

Timelines

The two appraisals have been scheduled as close to each other as possible, given advanced status of the primary prevention appraisal and constraints on capacity at ScHARR.