TECHNOLOGY ASSESSMENT REPORTS FOR THE HTA PROGRAMME

Strontium ranelate for the prevention of osteoporotic fractures in post-menopausal women with osteoporosis
FINAL PROTOCOL
November 2004

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B. Full title of research question

Strontium ranelate for the prevention of osteoporotic fractures in post-menopausal women with osteoporosis

C. Clarification of research question and scope

The objective of this assessment is to establish the clinical and cost effectiveness of strontium ranelate (Protelos, Servier Laboratories Ltd.) for the prevention of osteoporotic fractures in post-menopausal women with osteoporosis, and to provide guidance to the NHS in England and Wales.

The evidence for the clinical effectiveness of strontium ranelate for the prevention of osteoporotic fractures in post-menopausal women with osteoporosis will be reviewed systematically, as will any relevant published cost-effectiveness and cost-utility studies.

An economic model will be used to assess the cost-effectiveness of strontium ranelate initially in comparison with management strategies which do not use drugs affecting bone metabolism. Where head-to-head randomised controlled trials of strontium ranelate and other pharmaceutical interventions for osteoporosis exist, the relative cost-effectiveness compared with these drugs will be given.

The review will not only focus on differences between treatments in fracture rates, but will also aim to include any significant impacts that such treatments may have on health-related quality of life.

Data on mortality following an osteoporotic fracture will also be used to take into account number of deaths that occur as a direct consequence of a fracture.

The key outcome measures for the economic analysis will be the combined discounted direct NHS and social services costs of fractures and intervention for a cohort of patients, and the total discounted quality of life experienced and discounted life years gained accumulated by these patients.

Studies which include fractures as an outcome measure, but which have only published BMD data so far may be included if fracture data can be obtained from the study investigators.

If evidence allows, consideration will be given to adverse effects of treatments.

D. Report methods

Search strategy

The search will aim to identify all trials of strontium ranelate in osteoporosis. The following databases will be searched: Medline, Medline in Process, Embase, Science Citation Index (SCI), the Cochrane Library, NHS CRD DARE, NHS EED and HTA and OHE HEED. Searches will not be restricted by publication type or by study design as studies that do not meet the review inclusion criteria may be important in identifying further relevant papers and current research. A sample search strategy is provided below (Ovid Medline):

1 strontium ranelate.af
2 osseor.af
3 protelos.af
4 s12911.af
5 or/1-4

Current research registers (e.g. the National Research Register, Current Controlled Trials) will also be searched and relevant professional and research organisations contacted. Citation searches of key included studies will be undertaken using the SCI citation search facility, and the reference lists of included studies, sponsor submissions and relevant review articles will also be checked.

Inclusion criteria

Population: Post-menopausal women with osteoporosis who are considered to be at risk of osteoporotic fractures, including those who have and have not had a previous fracture
Intervention: Strontium ranelate
Comparators: Management strategies which do not use drugs affecting bone metabolism. If the evidence allows, strontium ranelate will be compared with the following drugs which affect bone metabolism: bisphosphonates, selective oestrogen receptor modulators, parathyroid hormone and calcitonin.
Outcomes: Vertebral and nonvertebral fractures (including hip, wrist and proximal humerus fractures); overall survival; adverse effects; cost; health-related quality of life.

Methodology
Randomised controlled trials. Economic evaluations.

Exclusion criteria

Studies in which patients were not Vitamin D replete and/or had insufficient calcium intake.
Studies considered methodologically unsound in terms of either study design or method used to assess fractures, or which do not report results in the necessary detail.
Studies of multi-interventional therapies where the effect of strontium ranelate could not be separated out.

Data extraction strategy
Sifting of retrieved studies will be carried out in three stages: first titles, then abstracts and finally full studies, excluding at each step studies that do not satisfy the inclusion criteria.

Data will be extracted by one researcher using a standardised data extraction form; any studies that give rise to uncertainty will be reviewed by a second researcher, and any disagreements will be resolved by discussion.

Quality assessment strategy
The methodological quality of all trials that meet the inclusion criteria will be assessed using the tool developed by Gillespie et al (see Appendix 1 below). This tool was selected because it was intended specifically for the assessment of randomised or quasi-randomised trials of interventions designed to prevent fractures associated with osteoporosis. If appropriate, quality will also be assessed using the Downs and Black tool.
Economic analysis of strontium ranelate (including any provided in the company submission) will be reviewed using assessed in relation to the checklist provided by Drummond and Jefferson. (BMJ 3 August 1996; 313:275-283).

Methods of analysis/synthesis
Meta-analysis will be undertaken if a number of RCT trials report fracture outcome data, and are comparable in terms of populations, interventions and outcomes. ReviewManager software will be used, and a mathematical model will be developed to synthesise the available data on fracture rates and quality of life of patients treated with each different intervention regime.

Methods for estimating quality of life, costs and cost-effectiveness and/or cost/QALY

The economic model used for this assessment will be an updated version of that constructed for the NICE review 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. This model will be consistent with those models used for other appraisals of osteoporosis treatments being developed concurrently.

Cost and utility data from published sources associated with different types of osteoporotic fracture will be incorporated into the above model in order to allow economic, as well as clinical, implications of treatment to be assessed.

The key model outputs will be as follows:

- Discounted incremental costs and discounted incremental quality adjusted life years gained for a cohort of patients. These will be calculated for both strontium ranelate and management without the use of drugs affecting bone metabolism, allowing the calculation of the cost-effectiveness of strontium ranelate versus management without drugs affecting bone metabolism.
- Where head-to-head randomised controlled trials have been conducted comparing strontium ranelate and other pharmaceutical interventions for osteoporosis, incremental cost-effectiveness analyses will be provided and a provisional hierarchical order of interventions will also be produced. A sensitivity analysis will be undertaken to identify the key parameters that determine the cost-effectiveness of the treatments, with the objective of identifying how robust the results of the economic analysis are, given the current level of evidence.

E. Handling the company submission(s)

The industry dossier will be used as a source of data, looking for studies that meet the inclusion criteria (RCTs/other effectiveness as well as cost effectiveness and cost utility studies). A critical appraisal of any industry models submitted, including the strengths and weaknesses and the implications of different assumptions, will be undertaken. The cost-effectiveness results from the company submission will be compared with those produced by the academic team.

Any 'commercial in confidence' data taken from the company submission will be underlined in the HTA report (followed by an indication of the relevant company name e.g. in brackets)

F. Project management

a. **Timetable/milestones** - submission of:

Draft protocol:	8th November 2005
Finalised protocol:	22nd November 2005
Progress report:	4th February 2005
Complete and near final draft sent to external reviewers and NICE Technical Leads	1st May 2005
Final assessment report:	6th June 2005

b. **Competing interests**

None

c. **External review**

The Technology Assessment Report will be subject to external review by at least two experts acting on behalf of the NHS HTA Programme. These referees will be chosen according to academic seniority and content expertise and will be agreed with NCCHTA. We recognise that the NICE secretariat and Appraisal Committee will undertake methodological review. In addition, an external methodological referee will be asked to review the report on behalf of the HTA Programme. Referees will review a complete and near final draft of the TAR and will understand that their role is part of

external quality assurance. Referees will be required to sign a copy of the NICE Confidentiality Acknowledgement and Undertaking which we will hold on file. Comments from referees and the Technical lead, together with our responses will be made available to NCCHTA in strict confidence for editorial review and approval.

H. Appendices

Appendix 1: Quality Assessment Scale

(after Gillespie WJ, Henry DA, O'Connell DL, Robertson J. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis (Cochrane Review). The Cochrane Library 1999)

	Score
Was randomisation to the study groups blinded?	
not randomised	0
states random but no description or quasi-randomised *(i.e. allocation by date of birth, hospital record no, admission dates, alternately etc)*	1
small but real chance of disclosure of assignment *(eg sealed envelopes)*	2
method does not allow disclosure of assignment *(eg assigned by telephone communication, or by indistinguishable drug treatments randomly precoded by centralised pharmacy)*	3
Were assessors of outcome blinded to treatment status?	
not mentioned	1
moderate chance of unblinding of assessors	2
action taken to blind assessors, or outcomes such that bias is unlikely	3
Were the outcomes of patients who withdrew described and included in the analysis?	
not mentioned or states number of withdrawals only	
states numbers and reasons for withdrawal, but analysis unmodified	1
primary analysis based on all cases as randomised	2
	3
Comparability of treatment and control groups at entry	
large potential for confounding or not discussed	1
confounding small; mentioned but not adjusted for	2
unconfounded; good comparability of groups or confounding adjusted for	3
For hip or other appendicular skeleton fracture	
not applicable	0
no confirmation of diagnosis	1
x-ray confirmation of diagnosis	3
For vertebral fracture	
not applicable	0
inadequately described method	1
radiological method: uses anterior/posterior height ratio	2
radiological method: uses anterior, middle and posterior height in criteria OR reports radiologically confirmed clinical events only	3
Total methodology score (actual score as %age of possible score)	