SUBMISSION TO THE NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE FOR THE APPRAISAL

"STRONTIUM RANELATE FOR THE PREVENTION OF POSTMENOPAUSAL OSTEOPOROTIC FRACTURES"

ON BEHALF OF SERVIER LABORATORIES LTD.

Executive Summary

Current first line therapy in the management of Osteoporosis in England and Wales is treatment with bisphosphorates. These have been shown to be effective in clinical trials. However, problems with compliance and persistence on treatment due to complex administration regimes and the rate of gastrointestinal adverse events means that many patients who should be treated are either never put on bisphosphorates or quickly cease to take them. Strontium ranelate (Protelos) is a new, well-tolerated intervention for the prevention of fractures in patients with post-menopausal osteoporosis. Strontium ranelate is an alternative first line therapy that shows comparable efficacy to the bisphosphorates but does not have the same problems of complicated administration or GI risk.

Strontium ranelate is the only product currently available with a dual mechanism of action, increasing bone formation and decreasing bone resorption simultaneously, rebalancing bone turnover in favour of bone formation. Pre-clinical studies show improvements in bone strength and volume, clinical studies show that the crystal structure mineralisation and microarchitecture of bone is preserved. Phase III trials show reductions in risk of both vertebral and peripheral fractures comparable to that achieved by bisphosphorates in clinical trials. Strontium ranelate trials are unusual in giving direct, significant evidence of efficacy in preventing peripheral fractures and unique in demonstrating efficacy in a population of people aged over 80 years.

Two phase III studies were conducted simultaneously. These were:

- SOTI (Spinal Osteoporosis therapeutic intervention) which was a double blind placebo controlled trial in 12 countries. It randomised 1649 post-menopausal women with low BMD and at least one vertebral fracture to either 2g strontium ranelate per day, or placebo, for three years. The primary outcome measured was new vertebral fracture. Strontium ranelate reduced the relative risk of new vertebral fracture

by 49% in year 1 and 41% over 3 years. For clinical vertebral fracture the reduction was 38%.

- TROPOS (Treatment of Peripheral Osteoporosis) which was a double blind placebo controlled trial in 12 countries. It randomised 5091 women over the age of 70 at high risk of fracture to either 2g strontium ranelate per day or placebo. The primary outcome measured was the effect on osteoporosis related peripheral (non vertebral) fractures. Strontium ranelate reduced the risk of such fractures by 16% over a minimum of three years. When the analysis was confined to major osteoporotic peripheral fractures the reduction was 19%. An EMEA requested analysis in the patient population over 74 years and defined as osteoporotic at baseline showed that strontium ranelate reduced the relative risk of hip fracture in this group by 36%.

  The efficacy of strontium ranelate is comparable to that of bisphosphorates.

Summary of results from studies of alternative treatments for osteoporosis – vertebral and clinical vertebral fractures

Drug	Study	Risk profile of pts at baseline	Mean age (yrs)	Pts randomised	PBO	SR	ARR	NNT	Relative risk (95% CI)
Strontium ranelate 2g									
	SOTI Incidence of vertebral fracture	High: low BMD and prevalent vertebral fracture	69.3	1026	32.76%	20.92%	11.8%	8	0.59 (0.46-0.76)
	SOTI Incidence of clinical vertebral fracture	High: low BMD and prevalent vertebral fracture	69.3	1649	17.36%	11.26%	6.1%	16	0.62 (0.47- 0.83)
Alendronate 5 – 10 mg									
	FIT-1[35]	High: vertebral fractures	71	2027	15.00%	8.00%	7.00%	14	0.53 (0.41-0.68)
	FIT-2[57]	Low: no vertebral fractures	68	4432	3.80%	2.10%	1.70%	59	0.56 (0.39-0.8)
Risedronate 5 mg									
	VERT-US[37]	High (vertebral)	69	1641	16.30%	11.30%	5.00%	20	0.59 (0.43-0.82)
	VERT-MN[36]	High (vertebral)	71	816	29%	18.10%	10.90%	9	0.51 (0.36-0.73)

Summary of results from studies of alternative treatments for osteoporosis – non-vertebral fractures

Drug	Study	Risk profile of pts at baseline	Mean age (yrs)	No. of pts randomised	Fracture incidence		NNT	Relative risk (95% CI)
					Placebo	Drug		
Strontium ranelate 2g								
	TROPOS Non-Vertebral fracture	High: aged women, low BMD	77	5091	12.90%	11.20%	58.8	0.84 (0.70-1.0)
	Major osteoporosis-related fracture	High: aged women, low BMD	77	4932	8.9%	7.1%	55	0.81(0.66-0.98)
	Non-vertebral fracture in patients without a previous fracture	High: aged women, low BMD	77					0.75 (0.56-0.99)
Alendronate 5 – 10 mg								
	FIT-1	High (vertebral)	71	2027	14.70%	11.90%	35.7	0.8 (0.63-1.01)
	FIT-2	Low (no vertebral fracture)	68	4432	13.30%	11.80%	66.7	0.88 (0.74-1.04)
Risedronate 5 mg								
	VERT-US	High (vertebral)	69	1641	8.40%	5.20%	31.3	0.61(0.39-0.94)
	VERT-MN	High (vertebral)	71	816	16.00%	10.90%	19.6	0.67(0.44-1.04)

Cost effectiveness

Economic modelling using the model structure previously adopted by NICE demonstrates that use of strontium ranelate is cost effective, using £30,000 per QALY as a threshold. The tables below show the results of simulations from the model.

Table 0.3 The Cost-Effectiveness of strontium ranelate. Simulated For Women with Previous Fractures and a T-Score <–2.5.

Age Group	Cost incurred (£) [d]	QALYs accrued	Marginal Costs (£) [e]	Marginal QALYs [e]	Cost per QALY (£) (95% C I)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[d] Including drug acquisition costs, GP consultations and BMD scans.
[e] Compared with no treatment in women with sufficient calcium and vitamin D intakes.

Table 0.4 The Cost-Effectiveness of Strontium Ranelate. Simulated for Women at Double Fracture Risk with previous Fractures and a T-Score of –2.5.

Age Group	Cost incurred (£) [d]	QALYs accrued	Marginal Costs (£) [e]	Marginal QALYs [e]	Cost per QALY (£) (95% C I)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[d] Including drug acquisition costs, GP consultations and BMD scans.
[e] Compared with no treatment in women with sufficient calcium and vitamin D intakes.

Impact on the NHS

Most new spending on strontium ranelate will be on treating patients who have failed on existing medications, as these patients would have otherwise gone without effective treatment. Those patients who are started on strontium ranelate will add little to the total cost of treatment as those patients would otherwise have been treated with a bisphosphorate. On this basis it is expected that the net cost to the NHS of strontium ranelate would be about £3 million in 2005, £7.8 million in 2006 and £12.8 million in 2007.