PUBLIC SUMMARY DOCUMENT

Product: Strontium ranelate, sachets, 2 g, Protos®

Sponsor: Servier Laboratories (Australia) Pty Ltd

Date of PBAC Consideration: July 2007

1. Purpose of Application

The submission requested an extension to the recommended listing of strontium to include women aged 70 years or older with low bone mineral density (BMD) T-score of -3.0 or worse and without prevalent fracture.

2. Background

At the July 2005 meeting, the PBAC recommended strontium ranelate for initial treatment as the sole anti-resorptive agent for established post-menopausal osteoporosis in patients with fracture due to minimal trauma. The PBAC recommended listing on a cost-minimisation basis compared to alendronate for the outcome of morphometric vertebral fracture. The equi-effective doses were strontium 2 g daily and alendronate 70 mg weekly. *(See also Public Summary Document for July 2005).*

At the November 2006 meeting, the PBAC rejected an application for primary prevention of post-menopausal osteoporosis because of uncertain clinical benefit and uncertain and unacceptable cost effectiveness. *(See also Public Summary Document for November 2006).*

At the March 2007 PBAC meeting, the PBAC deferred a minor submission for the current listing to include women ≥70 years with a low bone mineral density (BMD) T-score ≤-3.0 without prevalent fracture to allow a complete analysis to occur. *(There is no Public Summary Document for the March 2007 consideration).*

3. Registration Status

Strontium ranelate was TGA registered on 21 June 2005 for treatment of postmenopausal osteoporosis to reduce the risk of fracture.

4. Listing Requested and PBAC's View

Authority required

Initial treatment as the sole PBS-subsidised anti-resorptive agent for osteoporosis in women aged 70 years or older and with a BMD T-score of -3.0 or less. The initial authority application must state the date, site (femoral neck or lumbar spine) and score of the qualifying BMD measurement.

Continuing treatment as the sole anti-resorptive agent for osteoporosis in women aged 70 years or older and with a BMD T-score of -3.0 or less, where the patient has previously been issued with an authority prescription for this drug.

The PBAC agreed to the proposed wording and noted that strontium is available under the streamlined authority arrangements.

5. Clinical Place for the Proposed Therapy

Thirty percent (30%) to fifty percent (50%) of women will suffer a fracture related to osteoporosis in their lifetime. Fractures increase morbidity and mortality and impose a financial burden on the community. The overall mortality is about 20% in the first 12 months after hip fracture.

Strontium ranelate has a dual effect on bone metabolism, both increasing bone formation and decreasing bone resorption. Strontium ranelate would provide an alternative treatment for osteoporotic women considered to have a similar risk of fracture as women who have had a prior fracture due to minimal trauma.

6. Comparator

The submission nominated alendronate as the main comparator. The listing sought for strontium ranelate is the same as that of alendronate, with the exception that strontium is for women, while alendronate is approved for use in both men and women.

7. Clinical Trials

The submission presented an indirect comparison between strontium and alendronate, using placebo as a common reference.

The basis of the comparison was two multi-centre, multinational, randomised, double-blind, parallel group, placebo-controlled trials. The TROPOS trial assessed the efficacy of a 2g daily dose of strontium ranelate compared to placebo in reducing the incidence of osteoporosis-related peripheral fracture in osteoporotic postmenopausal women at risk of fracture (femoral neck BMD ≤ 0.600 g/cm^2). The FIT/FIT-2 trial assessed the efficacy of a 5-10mg/day dose of alendronate compared to placebo in reducing the risk of fracture in osteoporotic women who were postmenopausal for at least 2 years with femoral neck BMD ≤ 0.680 g/cm^2.

The baseline characteristics of the two studies differed in that the women in TROPOS were on average 9 years older (mean 77years compared to 68 years in FIT-2), had a lower BMD (0.552 g/cm2 in TROPOS and 0.593 g/cm2 in FIT-2) and had more prevalent fractures at baseline. In TROPOS, approximately 30% and 55% of patients had a prevalent vertebral or any osteoporosis related fracture at baseline respectively; in FIT-2, no patients had a prevalent vertebral fracture and 36% had a prevalent peripheral fracture at baseline.

These trials have been published at the time of submission as follows:

Trial/First author	Protocol title/Publication title	Publication citation
Reginster *et al.*	Strontium ranelate reduces the risk of non-vertebral fractures in postmenopausal women with osteoporosis: Treatment Of Peripheral Osteoporosis (TROPOS).	*Journal of Clinical Endocrinology Metabolism* 2005; 90(5): 2816-22.
Cummings *et al.*	Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures.	*JAMA* 1998; 280: 2077-82.

In addition to the intention-to-treat analysis (ITT), two *post hoc* sub-group analyses were undertaken for the TROPOS trial.

Primary prevention subgroup
This subgroup was defined as patients having no prevalent osteoporosis-related peripheral or prevalent vertebral fracture at inclusion in the Fracture International Run-in for Strontium Trials (FIRST) study, which was a calcium and vitamin D normalisation protocol, being a run-in study to TROPOS. This group was considered the main subgroup of interest for the submission as it represented the target population: the "primary prevention" of fractures due to osteoporosis in postmenopausal women. There were two subsets in this subgroup:
a) peripheral fractures - patients having at least one post-baseline measurement for occurrence of peripheral fractures (2,687 women, comprising 54% of ITT population)
b) vertebral fractures - patients with one assessable vertebral x-ray at baseline and at least one assessable post-baseline vertebral x-ray between Month 0 and Month 36 (1,960 women, comprising 40% of ITT).

High risk subgroup
This subgroup was defined according to the age range (≥ 74 years) with low femoral neck BMD (T-score ≤ -3.0) at inclusion. This subgroup represented 40% of the ITT analysis. At inclusion, approximately one third of patients had at least one prevalent vertebral fracture and about 40% had a peripheral fracture. The efficacy from this subgroup was supportive.

The subgroup of patients with a BMD <-2.5 from the FIT-2 study was used for comparison with the TROPOS study results.

8. Results of Trials

The primary endpoint for the TROPOS trial was the incidence of osteoporosis-related fractures (non-vertebral). The primary endpoint for the FIT-2 trial was new clinical fractures (vertebral and non-vertebral). Vertebral fractures were assessed in both studies as a secondary outcome. The ITT results of the key trials are summarised in the table below.

Summary of the ITT results of the indirect comparison: TROPOS trial vs. FIT-2 trial

Endpoints	TROPOS			FIT-2			Indirect estimate of effect RR (strontium v alendronate) (95% CI)
	Treatment effect RR (95% CI)	Strontium N (%)[a]	Placebo N (%)[a]	Placebo N (%)	Alendronate N (%)	Treatment effect RR (95% CI)	
ITT Populations from TROPOS and FIT-2							
Clinical OP fractures	0.84 (0.72, 0.98)	321/2479 (12.9%)	375/2453 (15.3%)	312/2218 (14.1%)	272/2214 (12.3%)	0.87 (0.75, 1.02)	0.97 (0.78,1.20)
Morphometric vertebral fractures	0.61 (0.51, 0.73)	201/1817 (11.1%)	321/1823 (17.6%)	78/2077 (3.8%)	43/2057 (2.1%)	0.56 (0.39, 0.80)	1.09 (0.73,1.63)
Non-vertebral fractures	0.84 (0.71, 1.00)	233/2479 (9.4%)	276/2453 (11.3%)	294/2218 (13.3%)	261/2214 (11.8%)	0.89 (0.76, 1.04)	0.94 (0.75,1.19)
Major OP compared to clinical OP	0.81 (0.66, 0.98)	181/2479 (7.3%)	225/2453 (9.2%)	312/2218 (14.1%)	272/2214 (12.3%)	0.87 (0.75, 1.02)	0.93 (0.72,1.20)
Hip fractures	0.85 (0.61, 1.19)	62/2479 (2.5%)	74/2453 (3.0%)	24/2218 (1.1%)	19/2214 (0.9%)	0.79 (0.44, 1.43)	1.08 (0.55,2.12)

[a] Fracture incidence calculated (n/N)
OP = osteoporotic

The PBAC also considered additional indirect comparisons of the primary prevention subgroup from TROPOS with BMD <-2.5 subgroup from FIT-2 and the high-risk subgroup (age >74, BMD <-3.0) from TROPOS with BMD <-2.5 subgroup from FIT-2. In total, the results of twelve indirect comparisons were considered.

The submission claimed that, overall, the indirect comparison showed that fracture risk is similar for both drugs in the ITT population and the post hoc subgroup populations. The PBAC had already accepted that strontium ranelate was efficacious in women with prior fragility fracture on the basis of the SOTI trial. There was no conclusive evidence of a difference between strontium and alendronate but it should be noted that in the subgroup that was proposed as the basis of the new PBS listing the relative risk (RR) values tended to be closer to the null than those observed with alendronate treatment. It should also be noted that there were substantial differences in the baseline (placebo) risks between the trial populations, particularly for morphometric vertebral fracture. The latter was partly because X-rays were performed before entry in the FIT-2 trial, whereas they were done after entry in the TROPOS trial, and women in TROPOS were older and had lower bone mineral density.

The submission presented no formal indirect comparison of toxicity. The submission stated that based on the 2005 PBAC decision for secondary prevention "it is reasonable to accept that the safety profiles will once again be similar when used in women with low BMD and no prior fracture (primary prevention). The side effects reported during the TROPOS study and SOTI study with strontium supported this similarity. The same applied for the FIT-1 and FIT-2 studies with alendronate".

The PBAC noted that strontium treatment appears to be associated with more gastrointestinal adverse events than placebo and rises in creatinine kinase (CK) levels appeared more common. *More information on the comparative safety of alendronate and strontium, can also be found in the Public Summary Document for strontium for July 2005.*

See Recommendation and Reasons for PBAC's view.

Subsequent to this submission to PBAC, the Australian strontium Product Information has been updated with new information about the rises in creatinine kinase levels, viz: "Creatine phosphokinase (CPK) was systematically assessed at each visit in phase III studies. Without it having been associated with clinical muscular symptoms or other biological abnormalities, transient emergent increases (>3 times the upper limit of the normal range) in CPK (musculo-skeletal fraction) were reported in 1.4% and 0.6% of the strontium ranelate and placebo groups respectively. These values spontaneously normalised with no treatment change." (TGA Approved Product Information – May 2007)

9. Clinical Claim

The submission claimed that strontium ranelate (2g per day) was no worse than alendronate (70mg/weekly) in terms of effectiveness and toxicity.

See Recommendation and Reasons for PBAC's view.

10. Economic Analysis

The submission presented a cost minimisation analysis as the preliminary economic evaluation.

The equi-effective doses in the context of cost minimisation were strontium ranelate 2 g daily and alendronate sodium 70 mg weekly.

11. Estimated PBS Usage and Financial Implications

The likely number of patients/packs dispensed/year accounting for market share as necessary was estimated by the submission to be within the range 50,000 to 100,000 in Year 5. This was assuming that all patients continue treatment until the end of Year 5.

The financial cost/year to the PBS (excluding co-payments) was estimated by the submission to be within $10 – $30 million in Year 5. The overall market was not expected to grow or to grow more rapidly as a result of listing strontium ranelate.

12. Recommendation and Reasons

The PBAC recommended the listing of strontium as the sole PBS-subsidised antiresorptive agent for osteoporosis in a woman aged 70 years or older with a bone mineral density (BMD) T-score of -3.0 or less on a cost minimisation basis compared to alendronic acid, and where strontium ranelate 2 g daily is equivalent to alendronate sodium 70 mg weekly.

Although the PBAC accepted the claim that strontium was no worse than alendronic acid in terms of effectiveness and toxicity, the PBAC considered there was some remaining uncertainty associated with the conclusion given the difference in the populations in the indirect comparison of the TROPOS and FIT-2 trials which resulted from the differences in trial design and baseline characteristics. Further, the PBAC noted that long-term safety data on strontium are limited, and that while accepting osteonecrosis of the jaw is associated with bisphosphonates, noted this is a rare adverse event.

Recommendation

STRONTIUM RANELATE, sachet, 2 g, Protos®, Servier Laboratories (Australia) Pty Ltd

Add to the current listing:

Restriction:	Authority required Treatment as the sole PBS-subsidised antiresorptive agent for osteoporosis in a woman aged 70 years or older with a bone mineral density (BMD) T-score of -3.0 or less. The date, site (femoral neck or lumbar spine) and score of the qualifying BMD measurement must be documented in the patient's medical records when treatment is initiated.
Maximum Quantity:	28
Repeats:	5

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Strontium ranelate is an alternative to other drugs used to reduce the risk of fractures resulting from osteoporosis, such as bisphosphonates (alendronate, risedronate, etidronate) or raloxifene (NPS RADAR August 2007).