PUBLIC SUMMARY DOCUMENT

Product: Strontium Ranelate, sachet containing granules for oral suspension, 2 g, Protos®

Sponsor: Servier Laboratories (Australia) Pty Ltd

Date of PBAC Consideration: November 2006

1. Purpose of Application

The submission sought a new Authority Required PBS listing for initial and continuing treatment for the primary prevention of fractures due to osteoporosis in postmenopausal women.

2. Background

The PBAC had not previously considered a submission for strontium for the primary prevention of osteoporosis.

At the July 2005 meeting, the PBAC recommended an Authority Required listing for strontium for initial and continuing treatment for established postmenopausal osteoporosis in patients with fracture due to minimal trauma 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.

To date, the company had not accepted the prices offered and listing had not eventuated.

3. Registration Status

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

4. Listing Requested and PBAC's View

Authority required
Initial treatment for the primary prevention of fractures due to osteoporosis in postmenopausal patients of age 75 or greater with Bone Mineral Density (BMD) T-score of -3.0 or less.

Continuing treatment for osteoporosis where the patient has previously been issued with an authority prescription for this drug.

The PBAC noted that in its Pre-Sub-Committee Response the sponsor had redefined its requested listing to second-line, to restrict use to women 70 years of age or older with a BMD T-score -3.0 or less, who have a contraindication or intolerance to alendronate 70 mg.

5. Clinical Place for the Proposed Therapy

30% to 50% of women and 15-30% of men 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. It may be used in the primary prevention of fractures due to osteoporosis as well as in patients who have established osteoporosis that is defined as a fracture due to minimal trauma.

6. Comparator

The submission originally nominated placebo as the comparator. The PBAC noted that the proposal for the amended restriction wording supported placebo as the appropriate comparator. However, the PBAC considered that there was a considerable risk of usage outside the intended population. In view of this concern, a comparison with alendronate was important because it provided an informative frame of reference.

7. Clinical Trials

The submission presented the Treatment of Peripheral Osteoporosis (TROPOS) trial, a multicentre, multinational, randomised, double-blind, placebo-controlled study as the pivotal trial, which was designed to assess the efficacy of a 2 g daily dose of strontium in reducing the incidence of osteoporosis-related peripheral fracture as compared to placebo in osteoporotic postmenopausal women at risk (femoral neck BMD $\leq$ 0.600 g/cm^2 i.e. T-score < -2.5). The sample size for this study was 4932 women in the intention-to-treat (ITT) population with a mean follow-up of 2.5 years.

This trial had been published at the time of submission, as follows:

Trial/First author	Protocol title	Publication citation
TROPOS Reginster et al 2005	Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study.	Journal of Clinical Endocrinology and Metabolism 2005; 90 (5):2816-22.

Two *post hoc* sub-group analyses were undertaken.

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 intention-to-treat (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.

8. Results of Trials

The results from the TROPOS trial showed that the incidence over time of patients with at least one osteoporosis-related peripheral fracture was not statistically significant different to the incidence of peripheral fractures between strontium and placebo. In the *post hoc* high risk subgroup there was a statistically significant difference in peripheral fractures, favouring strontium in the key trial's primary analysis.

In the overall trial analysis there was a statistically significant difference in osteoporosis-related peripheral fractures, favouring strontium in the key trial's primary analysis, but there was no statistically significant difference in proximal femur fractures between strontium and placebo. In the overall trial analysis there was a statistically significant difference in any peripheral or clinical vertebral fracture, favouring strontium.

In the *post hoc* primary prevention subgroup and the high risk subgroup there was a statistically significant difference in osteoporosis-related peripheral fractures, favouring strontium. In the *post hoc* primary prevention subgroup there was no statistically significant difference in hip/proximal femur fractures between strontium and placebo. In the *post hoc* high risk subgroup there was a statistically significant difference in hip fractures between treatments.

As was seen with the overall trial population, there were more adverse events associated with the gastrointestinal and nervous systems in the strontium group compared with the placebo group for the high risk population.

For PBAC's comments on these results, *see Recommendation and Reasons.*

9. Clinical Claim

The submission claimed that strontium ranelate has significant advantages in effectiveness over placebo with similar or less toxicity.

For PBAC's view of this claim, *see Recommendation and Reasons.*

10. Economic Analysis

The submission presented a preliminary economic evaluation using a cost-effectiveness approach. The PBAC accepted this as valid. The resources included were drug costs and costs for fractures (hospital, nursing home, rehabilitation, GP visits).

The submission estimated that the trial-based incremental cost per extra fracture avoided would be in the range of $15,000 - $45,000. During the evaluation, the incremental cost per hip fracture avoided was calculated to be in the range $45,000 – $75,000.

The submission presented a modelled economic evaluation using a cost-utility approach. The PBAC accepted this as valid. The population in the model were women aged 75-110 with no prior fractures and a BMD T-score of ≤-3.0 at age 75. The resources included were drug costs and costs for fractures (hospital, nursing home, rehabilitation, GP visits).

The submission estimated that the base case modelled incremental discounted cost per extra quality adjusted life year (QALY) would be in the range $15,000 - $45,000.

11. Estimated PBS Usage and Financial Implications

The submission estimated that in Year 4 of listing the number of eligible patients would be > 200,000 and the financial cost to the PBS (excluding co-payments) would be in the range $10 – $30 million.

12. Recommendation and Reasons

The PBAC noted that in its Pre-Sub-Committee Response the sponsor had redefined its requested listing to second-line, to restrict use to women 70 years of age or older with a BMD T-score -3.0 or less, who have a contraindication or intolerance to alendronate 70 mg. Such a proposal supported placebo as the appropriate comparator. However, the PBAC considered there was a considerable risk of the risk of usage outside the intended population. In view of this concern, a comparison with alendronate was important because it provided an informative frame of reference.

There was no statistically significant difference in the incidence of peripheral fractures in the ITT population between strontium and placebo. Although there was a statistically significant difference in the *post hoc* high risk sub-group in the incidence of peripheral fractures, the PBAC was concerned that it may not be of clinical significance. In the type of fracture that the PBAC considered to be of most clinical importance, hip fracture, the statistically significant difference in the high risk subgroup result for hip fracture between strontium and placebo was considered marginal. The PBAC noted that there was no statistical difference between strontium and placebo for hip fracture in the ITT population. The PBAC thus considered that the evidentiary basis establishing strontium ranelate as superior to placebo in the requested high risk sub-group was weak.

The PBAC also noted the evidentiary basis presented in the Pre-Sub-Committee Response and during the hearing for establishing the equivalence of strontium and alendronate was incomplete and weak. Gastro-intestinal adverse effects, particularly diarrhoea are common in patients taking strontium ranelate. However, comparative toxicity of alendronate and strontium was not presented and thus it is unclear how many alendronate intolerant patients will tolerate strontium. Based on the comparison presented, the PBAC concluded there was no basis for a price advantage for strontium over alendronate.

The PBAC considered that there were a number of uncertainties that arose from the economic model. Because the model made some assumptions leading to an overestimate of the ICER,

and other assumptions leading to an underestimate, it was very uncertain what the net effect of these biases would be.

Therefore, the PBAC rejected the submission because of uncertain clinical benefit and uncertain and unacceptable cost effectiveness.

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

Servier will continue to work with the PBAC to identify options to achieve PBS-listing for strontium.