PUBLIC SUMMARY DOCUMENT
Product: Strontium ranelate, sachet containing granules for oral suspension, 2g, Protos®
Sponsor: Servier Laboratories (Australia) Pty Ltd
Date of PBAC Consideration: July 2012

1. Purpose of Application
To extend the current Authority Required (STREAMLINED) PBS listing for strontium for primary and secondary osteoporosis to include male patients.

2. Background
This was the first submission to be considered by the PBAC for the inclusion of male patients in the current restriction.

3. Registration Status
At the time of the PBAC consideration, strontium was not registered by the TGA for the requested indication.

4. Listing Requested and PBAC's View
Authority Required (STREAMLINED).
Treatment as the sole PBS-subsidised anti-resorptive agent for osteoporosis in a patient 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.

Treatment as the sole PBS-subsidised anti-resorptive agent for established osteoporosis in patients with fracture due to minimal trauma.
The fracture must have been demonstrated radiologically and the year of plain x-ray or CT-scan or MRI scan must be documented in the patient's medical records when treatment is initiated.

A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.

Note: Anti-resorptive agents in established osteoporosis include alendronate sodium, risedronate sodium, denosumab, disodium etidronate, raloxifene hydrochloride, strontium ranelate and zoledronic acid.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy
Osteoporosis is a condition which occurs when the bones lose minerals, such as calcium, more quickly than the body can replace them, leading to a loss of bone thickness (bone mass or density). As a result, bones become thinner and less dense, so that even a minor bump or accident can cause serious fractures.

While the prevalence of osteoporosis in males is lower than females, the submission noted that men were estimated to constitute appropriately 20% of all osteoporosis patients (Ringe, Dorst and Farahmand 2010).

The submission proposed that the place in therapy of strontium ranelate would be to provide males with an alternative to the bisphosphonates alendronate sodium and risedronate sodium which are currently PBS listed for the treatment of osteoporosis.

6. Comparator

The submission nominated a mixed comparator comprised of alendronate (including combinations with calcium and/or colecalciferol), risedronate (including combinations with calcium and/or colecalciferol) and zoledronic acid.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The submission was based on one head-to-head randomised trial comparing strontium ranelate to alendronate (Ringe et al 2010). The submission also presented a series of indirect comparisons:

- Strontium ranelate (MALEO) vs. risedronate (Boonen et al 2009) using placebo as the common comparator
- Strontium ranelate (MALEO) vs. zoledronic acid (Boonen et al 2011) using placebo as the common comparator
- Strontium ranelate (Ringe et al 2010) vs. zoledronic acid (Orwoll et al 2010) using alendronate as the common comparator

The table below details the published trials and associated reports presented in the submission:

Trial ID / First author	Protocol title / Publication title	Publication citation
Strontium ranelate vs. Placebo trials		
MALEO	The efficacy and safety of 2g strontium ranelate in the treatment of male osteoporosis. First report M0-M12 analysis. Protocol CL3-12911-032 (NP29799)	Servier study report (2010).
Kaufman et al (2011)	Strontium Ranelate In The Treatment Of Male Osteoporosis. One Year Results Of A Placebo Controlled Study.	Arthritis & Rheumatism 63: 1104 [Abstract only]
Kaufman et al (2012)	Efficacy and Safety of Strontium Ranelate in the Treatment of Male Osteoporosis	Osteoporosis International 23: S260 [Abstract only]
Strontium ranelate vs. Alendronate trials		
Ringe et al (2010)	Efficacy of strontium ranelate on bone mineral density in men with osteoporosis.	Arzneimittelforschung 60: 267–272
Bisphosphonate trials		
Boonen et al (2009)	Once-Weekly Risedronate in Men With Osteoporosis: Results of a 2-Year, Placebo Controlled, Double-Blind, Multicenter Study.	Journal of Bone and Mineral Research 24: 719–725

Kruk et al (2009).	LRP5 Polymorphisms and Response to Risedronate Treatment in Osteoporotic Men.	Calcified Tissue International 84: 171–179
Boonen et al (2011).	Once-yearly zoledronic acid in older men compared with women with recent hip fracture.	Journal of the American Geriatric Society 59: 2084–2090
Lyles et al (2007)	Zoledronic acid and clinical fractures and mortality after hip fracture.	New England Journal of Medicine 357: 1799–1809
Colon-Emeric et al (2004)	The Horizon recurrent fracture trial: design of a clinical trial in prevention of subsequent fractures after low trauma hip fracture repair.	Current Medical Research and Opinion 20: 903–910
Orwoll et al (2010)	Efficacy and safety of a once-yearly i.v. infusion of zoledronic acid 5mg versus a once-weekly 70-mg oral alendronate in the treatment of male osteoporosis: a randomized, multicenter, double-blind, active-controlled study.	Journal of Bone and Mineral Research 25: 2239–2250

8. Results of Trials

The primary outcome reported in all the trials was the change in BMD scores from baseline. Fractures were reported as secondary outcomes in all trials but none of the included studies were adequately powered to detect a difference in fracture outcomes between treatment arms.

Summary of BMD outcomes (% change in BMD from baseline to 12 months)

	Lumbar spine, WMD (95% CI)	Femoral neck WMD (95% CI)	Total hip WMD (95% CI)
Direct analyses			
STR vs. ALN	1.3 (0.16, 2.44)	-	0.8 (-0.16, 1.76)
Indirect analyses			
STR vs. RIS (indirect via PBO)	2.12 (0.34, 3.90)	2.00 (0.46, 3.54)	-
STR vs. ZOL (indirect via PBO)	-	1.45 (-0.51, 3.41)	-0.05 (-1.81, 1.71)
STR vs. ZOL (indirect via ALN)	2.07 (0.70, 3.43)	-	1.06 (0.07, 2.06)
STR vs. ZOL (indirect meta)	-	-	0.75 (-0.22, 1.73)

Abbreviations: ALN, alendronate; BMD, bone mineral density; CI, confidence interval; PBO, placebo; RIS, risedronate; STR, strontium; WMD, weighted mean difference; ZOL, zoledronic acid

Overall, the presented analyses suggested that strontium ranelate was non-inferior to alendronate, risedronate and zoledronic acid in terms of BMD (lower bound of the 95% CI greater than -1.5%). The only exception was a comparison of total hip BMD results between strontium ranelate and zoledronic acid (using a placebo common comparator) for which the lower bound of the 95% CI was less than -1.5% (WMD -0.05; 95% CI -1.81, 1.71). Differences between treatments generally favoured strontium ranelate. The exchangeability of trials was unclear given the differences in age, fracture history, calcium and vitamin D supplementation and possibly baseline BMD between studies.

The PBAC noted that changes in BMD scores with strontium ranelate treatment may not be directly comparable to changes in BMD scores with bisphosphonate treatment. As noted in

the strontium ranelate PI, approximately 50% of the change in BMD levels with strontium ranelate may be due to the strontium-content in bone (increased weight and x-ray absorption of strontium compared to calcium). The Pre-Sub-Committee Response (PSCR, p2) acknowledged that neither Ringe 2010 nor MALEO, made adjustments to account for the strontium content in bones. The PSCR argued that adjustment of BMD outcomes in strontium patients is not recommended, as the strontium artefact cannot be measured at the individual level.

The PBAC were unconvinced that BMD was a valid surrogate for fracture risk in patients treated with strontium, as strontium content in the bone could result in an overestimation of measured BMD due to the higher atomic weight of strontium compared to calcium. It was unclear the degree to which the BMD outcome could be confounded by the strontium effect.

A recent abstract of the MALEO trial was identified that presented a comparison of results with the female trials (Kaufman et al 2011).

Comparison of male (MALEO) and female (SOTI, TROPOS) results

Outcome	***MALEO N = 243***	***SOTI/TROPOS N = 6551***	***Difference[a]***
Lumbar spine BMD, % change at 12 months with strontium relative to placebo, mean (95% CI)	6.38 (4.1, 8.0)	7.04 (6.7, 7.4)	p = 0.442
Femoral neck BMD, % change at 12 months with strontium relative to placebo, mean (95% CI)	3.19 (1.8, 4.6)	3.52 (3.3, 3.8)	p = 0.655

Abbreviations: BMD, bone mineral density; CI, confidence interval
[a] p-value of the Student t-test

The PBAC noted that there were no statistically significant differences in BMD outcomes between males and females after 12-months treatment with strontium ranelate.

Treatment with strontium ranelate was associated with a lower incidence of short-term (12 month) adverse events compared to alendronate. Compared to placebo, treatment with strontium ranelate was associated with a higher incidence of serious adverse events (including iron deficiency anaemia, generalised urticaria and deep vein thrombosis) and adverse events leading to discontinuation (including dyspepsia, upper abdominal pain, toxic skin eruption, headache and deep vein thrombosis).

The PBAC noted that a Periodic Safety Update Report (PSUR) for strontium ranelate indicated that the sponsor is continuing to monitor the risk of eosinophilia (including drug toxicity syndrome and Steven-Johnson syndrome), lymphadenopathy, interstitial nephritis, pancreatic disorders, photosensitivity, hallucination, bone sarcoma, depression, insomnia and hypertension. The sponsor is also monitoring the following events as part of their risk management plan: hypersensitivity reactions, venous thromboembolic events, central nervous system events, blood creatine phosphokinase increase, rhabdomyolysis, hepatobiliary hypersensitivity, blood cytopenic disorders, and psychiatric disorders.

Potential safety concerns associated with bisphosphonate treatment include the risk of gastrointestinal side effects (including severe oesophageal ulceration), osteonecrosis of the jaw, renal impairment, atypical stress fractures, ocular symptoms, acute phase reactions, hypocalcaemia and musculoskeletal pain.

9. Clinical Claim

The submission described strontium ranelate as non-inferior (and possibly superior) in terms of BMD outcomes compared to bisphosphonates (alendronate, risedronate and zoledronic acid) in male patients. The submission claimed that strontium ranelate has a different safety profile to bisphosphonate therapies.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost-minimisation analysis of strontium ranelate compared to a mixed comparator comprised of alendronate, risedronate and zoledronic acid.

11. Estimated PBS Usage and Financial Implications

The likely number of patients was estimated by the submission to be less than 10,000 in Year 5, at an estimated net cost to the PBS of less than $10 million in Year 5 of listing.

12. Recommendation and Reasons

The PBAC recommended amending the PBS listing for strontium to include men aged 70 years of age or older with a Bone Mineral Density (BMD) T-score of -3 or less and men with established osteoporosis with fracture due to minimal trauma on a cost minimisation basis compared with alendronate alone. The equi-effective doses are 2 g strontium daily being equivalent to 70 mg alendronate weekly.

The PBAC noted that the submission had requested that the comparator be a mixed comparator, but the PBAC did not accept this proposal. The PBAC agreed that oral therapy is likely to be the comparator, and therefore did not consider zoledronic acid appropriate. The PBAC considered that alendronate was the market leader for both the primary and secondary prevention indications, noting that the submission estimated that alendronate made up more than 50% of the products that strontium would replace in practice. The PBAC recalled that when recommending for listing the alendronate combination products, no price advantage was given over alendronate alone, and the current price differential was an artefact of Government pricing policy. The PBAC further noted that the calcium and Vitamin D components in the alendronate combination products are not accounted for in the analysis. The comparator for strontium is alendronate alone as it is the therapy most likely to be replaced in practice.

The primary outcome of the trials presented in the submission was BMD. The results of the direct comparison vs alendronate and the indirect comparisons vs risedronate and zoledronic acid supported the claim of equivalence between strontium and the oral bisphosphonates. However, the PBAC noted that the studies were small and no fracture data had been presented which is the patient relevant outcome of interest.

The PBAC were unconvinced that BMD was a valid surrogate for fracture risk in patients treated with strontium, as strontium content in the bone could result in an overestimation of measured BMD due to the higher atomic weight of strontium compared to calcium. It was unclear the degree to which the BMD outcome could be confounded by the strontium effect. However, the PBAC considered that extending the listing of strontium to include men would be consistent with its previous acceptance of a relationship between BMD and fracture risk for other indications for strontium.

Recommendation:
STRONTIUM RANELATE, sachet containing granules for oral suspension, 2g

Amend the current listing as follows:

Restriction:	Authority Required (STREAMLINED). Treatment as the sole PBS-subsidised anti-resorptive agent for osteoporosis in a patient 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. Treatment as the sole PBS-subsidised anti-resorptive agent for established osteoporosis in patients with fracture due to minimal trauma. The fracture must have been demonstrated radiologically and the year of plain x-ray or CT-scan or MRI scan must be documented in the patient's medical records when treatment is initiated. A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body. Note: Anti-resorptive agents in established osteoporosis include alendronate sodium, risedronate sodium, denosumab, raloxifene hydrochloride, strontium ranelate and zoledronic acid.
Max qty:	28
Rpts:	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

The sponsor has no comments.