

6.06 STRONTIUM RANELATE
2g granules for oral suspension, 28 x 2g sachets
PROTOS®
SERVIER LABORATORIES

1 Purpose of Application

1.1 To support the continued listing of strontium ranelate for the treatment of severe established osteoporosis in patients unable to use other osteoporosis medications.

2 Current listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
STRONTIUM RANELATE 2g granules	28	5	\$52.00	Protos® Servier Laboratories
Restriction	Section 85 (General Schedule) Authority Required			
Condition	Severe established osteoporosis			
Clinical criteria	Patient must have fracture due to minimal trauma, AND Patient must not receive concomitant treatment with any other PBS-subsidised anti-resorptive agent for this condition, AND Patient must be at high risk of fracture, AND Patient must be unable to use other medications for the treatment of osteoporosis due to contraindications or intolerance.			
Prescriber instructions	The fracture must have been demonstrated radiologically and the year of plain x-ray or computed tomography (CT) scan or magnetic resonance imaging (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.			
Administrative advice	<u>Note</u> Anti-resorptive agents in established osteoporosis include alendronate sodium, risedronate sodium, denosumab, raloxifene hydrochloride, strontium ranelate and zoledronic acid.			

2.1 The submission requested the continued listing of strontium ranelate on a cost-effectiveness basis compared with best supportive care.

2.2 The evaluation suggested that it may be appropriate to consider adopting a specific definition of severe established osteoporosis into the restriction criteria. For example:

- World Health Organisation (WHO) definition: patients with a prior fragility fracture AND a bone mineral density (BMD) T-score of < -2.5; or
- Fracture Risk Assessment Tool (FRAX) definition: patients with a 10-year absolute fracture risk equivalent or greater than a patient with a prior fragility fracture and a BMD T-score of < -2.5.

The Pre-Sub-Committee Response (PSCR) proposed that the following additional clinical criterion could be included: *Patient must have BMD T-score \leq -2.5.*

- 2.3 The evaluation noted that the current PBS listing for strontium ranelate specified that patients must be unable to use other osteoporosis medications. This requirement could be interpreted as patients who are intolerant/contraindicated to any individual osteoporosis medication (i.e. may have other treatment options) or patients who are unable to use all osteoporosis medications (i.e. have no other treatment options). The submission assumed that most patients currently using strontium ranelate under the PBS will be intolerant/contraindicated to at least one first-line osteoporosis medication and therefore qualify under a less stringent interpretation of this requirement.
- The PSCR proposed specifying the medications that a patient must be unable to use for the treatment of osteoporosis due to contraindications or intolerance (the last clinical criterion in the restriction above); specifically; denosumab, a bisphosphonate, and raloxifene. The ESC noted the Administrative Advice in the strontium listing already included a list of other medications used in established osteoporosis.
 - The ESC noted that the current restriction did not define ‘intolerant’ or ‘contraindicated’.
- 2.4 In addition to the proposed change presented in the PSCR, the pre-PBAC response suggested that the following note could be included in the restriction: *Patients should be evaluated for cardiovascular risk prior to commencement of strontium ranelate and during ongoing treatment on a regular basis generally every 6 months. See Product Information for further details.*

For more detail on PBAC’s view, see section 7 “PBAC outcome”

3 Background

- 3.1 **TGA status at time of PBAC consideration:** Strontium ranelate was registered in June 2005 for the ‘treatment of postmenopausal osteoporosis’. The indication was extended in May 2012 to include the ‘treatment of male osteoporosis’. Due to safety concerns the indication was restricted to ‘severe (established) osteoporosis’ in May 2013; and further restricted to ‘patients unable to take other osteoporosis medications’ in March 2014.
- 3.2 There have been 12 previous PBAC considerations of strontium ranelate. At its most recent consideration in July 2014, the PBAC indicated that it was inclined to recommend the delisting of strontium ranelate from the PBS. However, the PBAC considered that it would be appropriate for the sponsor to have the opportunity to establish the cost-effectiveness of strontium ranelate in a restricted PBS population (patients with severe established osteoporosis unable to use other treatments due to contraindication or intolerance).

For more detail on PBAC’s view, see section 7 “PBAC outcome”

4 Clinical place for the proposed therapy

- 4.1 Osteoporosis is a condition which occurs when the bones lose minerals more quickly than the body can replace them leading to enhanced bone fragility (due to reduced bone mass and micro-architectural deterioration of bone tissue) and a consequent increase in fracture risk. Loss of bone strength occurs gradually over many years and usually shows no symptoms. The most common fractures occur at the hip, spine and wrist and can lead to increased mortality, long-lasting pain, reduced mobility and disability.
- 4.2 The submission did not clearly describe the proposed place in therapy for strontium ranelate but appeared to suggest that it may be used as a second-line treatment (in patients with other treatment options) or as a last-line treatment (in patients with no other treatment options). The PSCR argued that ‘it is not helpful to conceptualise the appropriate place in therapy with reference to “lines” of treatment; as strontium is appropriate only for patients who are contraindicated or intolerant to other therapies and not those who have failed to respond to these therapies.’
- 4.3 Expert advice presented in the submission (from the Institute of Bone and Joint Research and Menzies Research Institute) indicated that strontium ranelate has a role in the treatment of osteoporosis in patients experiencing adverse events characteristic of anti-resorptive therapy (e.g. bone pain, atypical fractures, osteonecrosis of the jaw) due to its different mode of action (promotes bone formation in addition to reducing bone resorption). All current first-line treatment options are anti-resorptives only.
- 4.4 The PSCR described the patients likely to use strontium:
- New patients who are contraindicated, intolerant to all available alternatives, including denosumab, oral and/or intravenous bisphosphonates, and raloxifene. ‘Based on recent dispensing data, this is a small but important population of approximately 300 patients per month, including around 100 who had received a previous treatment for osteoporosis. For these patients, strontium addresses an otherwise unmet clinical need’.
 - ‘In the case of the larger population of approximately 10,000 existing patients who are currently receiving and tolerating treatment with strontium the clinical place is more complex. Given the existing PBS restriction, these patients are assumed to be contraindicated or intolerant to at least one but not necessarily all of the available alternative therapies. Although such patients may have other options, it would be clinically inappropriate to force them to switch therapy based on population level data. For these patients, therefore, the clinical need for strontium arises from a continuity of care, within the criteria of the Phone Authority Restricted PBS listing implemented in October 1 2014.’
- 4.5 The ESC considered that the indication was unclear and that the submission did not provide sufficient justification of the clinical place and need for this drug for the majority of existing patients.
- 4.6 The pre-PBAC response reiterated the sponsor’s concerns that it would be clinically inappropriate to force existing, stabilised strontium patients to discontinue treatment based on population level data. The pre-PBAC response noted the extensive work undertaken in 2013 and 2014 to inform clinicians, through multiple channels, of

changes to the strontium TGA product information. The sponsor argued that these initiatives and the resulting impact on strontium utilisation over the past two years indicate that patients who are continuing on treatment are doing so based on an informed benefit-risk assessment on the part of their treating physician.

For more detail on PBAC's view, see section 7 "PBAC outcome"

5 Comparator

- 5.1 The submission nominated best supportive care as the primary comparator. This was considered the appropriate comparator for patients with no other treatment options.
- 5.2 The submission nominated denosumab as a secondary comparator. This was considered an appropriate comparator for patients who still have other treatment options. The evaluation considered that other potential comparators included the oral bisphosphonates (alendronate, risedronate).
- 5.3 The ESC considered that best supportive care was the appropriate comparator in patients contraindicated or intolerant to all other osteoporosis treatments. However, the ESC noted that these patients are probably a small proportion of the population currently using strontium ranelate on the PBS.

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician presented clinical case studies and discussed how strontium ranelate is currently used in practice. The clinician stated that strontium ranelate has a unique mode of action and maintains an important place in clinical therapy for those patients who are intolerant to other available drugs. It was further noted that if strontium ranelate was removed from the PBS, there would be some patients for whom no alternative treatment options would exist. The clinician also addressed other matters in response to the Committee's questions. The PBAC considered that the hearing did not add substantively to the evidence presented in the submission.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from health care professionals (6) and an organisation (1) via the Consumer Comments facility on the PBS website. The comments supported the retention of strontium ranelate on the PBS for patients with osteoporosis, without cardiovascular contraindications, who are unable to use other available treatments due to intolerance or concern about adverse events. The comments noted that there is a continuing role for strontium ranelate and that some patients could be disadvantaged if it was removed from the PBS.

- 6.3 The PBAC noted the advice received from Osteoporosis Australia supporting the continued availability of strontium ranelate on the PBS for patients with osteoporosis who are either currently taking the medication, or for those patients who are intolerant to other osteoporosis drugs and there is a low risk of cardiovascular disease. The advice also noted that strontium ranelate provides a different mode of administration, as a soluble powder, compared with other treatments. The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical trials

- 6.4 The submission was based on a series of direct and indirect comparisons between strontium ranelate and nominated comparators:
- Direct comparison of fracture outcomes with strontium ranelate vs. placebo in patients with postmenopausal osteoporosis (SOTI, TROPOS).
 - Direct comparison of BMD outcomes with strontium ranelate vs. placebo in patients with male osteoporosis (MALEO).
 - Indirect comparison of fracture outcomes with strontium ranelate (SOTI, TROPOS) vs. denosumab (FREEDOM) using a placebo common comparator in patients with postmenopausal osteoporosis.
 - Indirect comparison of BMD outcomes with strontium ranelate (MALEO) vs. denosumab (ADAMO) using a placebo common comparator in patients with male osteoporosis.
- 6.5 Two additional studies (Ringe et al 2010, DIRECT) were considered as supportive evidence only during the evaluation.
- 6.6 Details of the trials presented in the submission are provided in the table below.

Table 1: Trials and associated reports included in the submission

Trial ID	Protocol title/ Key publication title	Publication citation
Strontium ranelate trials		
NP08338 (SOTI)	Servier Clinical Study Report (2003). SOTI: Spinal Osteoporosis Therapeutic Intervention. The effects of a three-year oral administration of S12911 on the incidence of new vertebral fractures in osteoporotic postmenopausal women. A multicentre controlled study	Internal study report
	Servier Clinical Study Report (2006). SOTI: Spinal Osteoporosis Therapeutic Intervention. The effects of a four-year oral administration of S12911 on the incidence of new vertebral fractures in osteoporotic postmenopausal women. A multicentre controlled study. Fifth year of the study, after treatment switch	Internal study report
	Key publication: Meunier et al (2004). The Effects of Strontium Ranelate on the Risk of Vertebral Fracture in Women with Postmenopausal Osteoporosis	New England Journal of Medicine 350: 459-468
NP08340 (TROPOS)	Servier Clinical Study Report (2003). TROPOS: Treatment of Peripheral Osteoporosis. The effects of a three-year oral administration of S12911 on the incidence of peripheral fractures in osteoporotic postmenopausal women. A multicentre controlled study.	Internal study report
	Servier Clinical Study Report (2006). The effects of a five-year oral administration of S12911 on the incidence of peripheral fractures in osteoporotic postmenopausal women. A multicentre controlled study. Fifth year of the study	Internal study report

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Trial ID	Protocol title/ Key publication title	Publication citation
	Key publication: 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 90: 2816-2822
SOTI/ TROPOS	Kanis et al (2011). A meta-analysis of the effect of strontium ranelate on the risk of vertebral and non-vertebral fracture in postmenopausal osteoporosis and the interaction with FRAX.	Osteoporosis International 22: 2347-2355
	Reginster et al (2012). Maintenance of Antifracture Efficacy over 10 Years with Strontium Ranelate in Postmenopausal Osteoporosis	Osteoporosis International 23: 1115-1122
	Kanis et al (2013). A meta-analysis of the effect of strontium ranelate on the risk of vertebral and non-vertebral fracture in postmenopausal osteoporosis and the interaction with FRAX: A multivariate analysis to examine the impact of severe osteoporosis and contraindications	Confidential report (part of sponsor's response to EMA)
NP29799 (MALEO)	Servier Clinical Study Report (2010). The efficacy and safety of 2g strontium ranelate in the treatment of male osteoporosis. First year of study	Internal study report
	Key publication. Kaufman et al (2013). Efficacy and Safety of Strontium Ranelate in the Treatment of Osteoporosis in Men	Journal of Clinical Endocrinology and Metabolism 98: 592-601
Ringe (2010)	Key publication. Ringe et al (2010). Efficacy of Strontium Ranelate on Bone Mineral Density in Men with Osteoporosis	Arzneimittelforschung 60: 267-272
Denosumab trials		
FREEDOM	Key publication. Cummings et al (2009). Denosumab for the Prevention of Fractures in Postmenopausal Women with Osteoporosis	New England Journal of Medicine 361: 756-765
ADAMO	Key publication. Orwoll et al (2012). A Randomized, Placebo-Controlled Study of the Effects of Denosumab for the Treatment of Men with Low Bone Mineral Density	Journal of Clinical Endocrinology and Metabolism 97: 3161-3169
DIRECT	Key publication. Nakamura et al (2014). Fracture Risk Reduction with Denosumab in Japanese Postmenopausal Women and Men with Osteoporosis: Denosumab Fracture Intervention Randomized Placebo Controlled Trial (DIRECT)	Journal of Clinical Endocrinology and Metabolism 99: 2599-2607

6.7 The key features of the included trials are summarised in the table below.

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Key outcomes	Use in modelled evaluation
Strontium ranelate vs. placebo						
SOTI	1,649	MC, R, DB, PG 4 years	Low	Postmenopausal osteoporosis at increased risk of vertebral fracture	Fractures (3 year)	Not used
TROPOS	5,091	MC, R, DB, PG 5 years	Low	Postmenopausal osteoporosis	Fractures (3 year)	Not used
MALEO	261	MC, R, DB, PG 2 years	Low	Male osteoporosis	BMD	Not used
Meta-analysis	6,374	Includes subgroup analysis of SOTI and TROPOS based on disease severity and cardiovascular contraindications				Fracture outcomes
Denosumab vs placebo						
FREEDOM	7,868	MC, R, DB, PG 3 years	Low	Postmenopausal osteoporosis	Fractures (3 year)	Not used
ADAMO	242	MC, R, DB, PG 1 year	Low	Males with low BMD	BMD	Not used

Abbreviations: BMD, bone mineral density; DB, double blind; MC, multi-centre; PG, parallel-group; R, randomised.
Source: compiled during the evaluation.

- 6.8 The submission acknowledged that the trial populations were not representative of the current PBS population and therefore presented subgroup analyses assessing the impact of disease severity and cardiovascular risk factors on fracture outcomes. No analysis was presented to assess the impact of shifting place in therapy (i.e. from first-line treatment to second-line or last-line treatment).
- 6.9 The submission acknowledged heterogeneity between the SOTI and TROPOS trials which appeared to be primarily due to differences in trial populations due to the SOTI trial enrolling patients with an increased risk of vertebral fracture.
- 6.10 The submission also acknowledged differences in patient (e.g. fracture history, baseline BMD T-scores) and study characteristics (e.g. calcium and Vitamin D supplementation, differences in recruitment periods) between the strontium ranelate and denosumab trials which may have limited the exchangeability of studies included in the indirect analyses. The PSCR acknowledged that the trials were probably not sufficiently exchangeable to justify their inclusion in an indirect comparison but justified their inclusion given the absence of any better quality comparative evidence.

Comparative effectiveness

6.11 The following table presents a direct comparison of strontium ranelate vs. placebo.

Table 3: Fracture outcomes with strontium ranelate vs. placebo

Trial	Strontium n/N (%)	Placebo n/N (%)	RR (95% CI)	HR (95% CI) ^a	RD (95% CI)
Morphometric vertebral fractures					
SOTI (3 year)	139/719 (19.3%)	222/723 (30.7%)	0.63 (0.52, 0.76)	0.59 (0.48, 0.73)	-0.11 (-0.16, -0.07)
TROPOS (3 year)	202/1817 (11.1%)	321/1823 (17.6%)	0.63 (0.54, 0.74)	0.61 (0.51, 0.73)	-0.06 (-0.09, -0.04)
Meta-analysis SOTI/TROPOS (3 years) I ² = 0% [RR], 74% [RD]			0.63 (0.56, 0.71)	0.60 (0.52, 0.69)	-0.09 (-0.13, -0.04)
Clinical vertebral fractures					
SOTI (3 year)	75/719 (10.4%)	117/723 (16.2%)	0.64 (0.49, 0.85)	0.62 (0.47, 0.83)	-0.06 (-0.09, -0.02)
TROPOS (3 year)	119/1817 (6.5%)	138/1823 (7.6%)	0.87 (0.68, 1.10)	0.85 (0.67, 1.09)	-0.01 (-0.03, 0.01)
Meta-analysis SOTI/TROPOS (3 years) I ² = 61% [RR], 84% [RD]			0.75 (0.56, 1.00)	0.75 (0.62, 0.92)	-0.03 (-0.08, 0.02)
Clinical non-vertebral fractures					
SOTI (3 year)	112/719 (15.6%)	122/723 (16.9%)	0.92 (0.73, 1.17)	0.91 (0.71, 1.18)	-0.01 (-0.05, 0.03)
TROPOS (3 year)	233/2479 (9.4%)	276/2453 (11.3%)	0.84 (0.71, 0.99)	0.84 (0.71, 1.00)	-0.02 (-0.04, -0.00)
Meta-analysis SOTI/TROPOS (3 years) I ² = 0% [RR], 0% [RD]			0.86 (0.75, 0.99)	0.84 (0.72, 0.98)^b	-0.02 (-0.03, -0.00)
Clinical hip fractures					
SOTI (3 year)	NR	NR	-	-	-
TROPOS (3 year)	62/2479 (2.5%)	74/2453 (3.0%)	0.83 (0.59, 1.16)	0.85 (0.61, 1.19)	-0.01 (-0.01, 0.00)
Meta-analysis SOTI/TROPOS (3 years)			-	0.95 (0.70, 1.28)	-

Abbreviations: CI, confidence interval; HR, hazard ratio; NR, not reported; RD, risk difference; RR, relative risk.

Values in bold represent statistically significant differences observed between treatment groups.

^a Hazard ratios were based on Cox Proportional Hazards models adjusted for age, country, prior vertebral fracture and lumbar spine BMD in the SOTI trial and age, country, body mass index and femoral neck BMD in the TROPOS trial. Hazard ratios for the meta-analyses were based on a Poisson regression model adjusted for age, treatment exposure and calculated 10-year probability of fracture.

^b It is unclear whether the definition of a non-vertebral fracture used in the meta-analysis is consistent with the definitions used in each of the individual trials.

Source: Table B-33 (p 52), Table B-35 (p 54), Table B-49 (p 63), Table C-4 (p 79), Table C-5 (p 79), Table C-6 (p 79) of the submission

- 6.12 Treatment with strontium ranelate was associated with a statistically significant reduction in morphometric vertebral fractures compared to placebo. Strontium ranelate was also associated with a statistically significant reduction in clinical vertebral fractures (in a population at increased risk of vertebral fracture) and a borderline statistically significant reduction in non-vertebral fractures. Treatment with strontium ranelate was not associated with a reduction in hip fracture.
- 6.13 There were incomplete fracture outcome data available for the SOTI and TROPOS trials beyond 3-years (nominated time point for the primary outcome). There were also substantial differences in vertebral fracture rates between trials which was reflective of clinical heterogeneity between studies due to the SOTI trial enrolling a patient population at increased risk of vertebral fracture.

- 6.14 Longer term data from observational follow-up studies (up to 10 years) suggested that the incidence of fracture was similar to estimates reported during the randomised periods and remained substantially lower than predicted from risk estimates.
- 6.15 Strontium ranelate was associated with statistically significant increases in BMD measures compared to placebo in males with osteoporosis. The submission acknowledged the difficulties in interpreting the clinical importance of BMD outcomes but noted that these results were similar to those previously shown to be associated with fracture risk reduction in women with postmenopausal osteoporosis. Therefore, the submission argued that, in the absence of any known gender-specific difference in treatment effect, it may be acceptable to assume a similar relative reduction in fracture risk with men and women. The evaluation considered that this argument appeared reasonable.
- 6.16 Subgroup analyses of strontium ranelate vs. placebo are presented in the following table.

Table 4: Subgroup analyses based on severity and cardiovascular risk factors

Outcome	Any cardiovascular risk factor HR (95% CI) ^a , N = 3,187	No cardiovascular risk factor HR (95% CI) ^a , N = 3,187
Morphometric vertebral fracture	0.61 (0.50, 0.74)	0.60 (0.49, 0.72)
Clinical vertebral fractures	0.79 (0.60, 1.03)	0.74 (0.56, 0.97)
Any clinical fracture ^b	0.81 (0.68, 0.96)	0.84 (0.71, 1.00)
Any clinical osteoporotic fracture ^b	0.78 (0.66, 0.93)	0.84 (0.71, 1.00)
Hip fracture	0.94 (0.61, 1.45)	0.96 (0.63, 1.46)
Outcome	Severe osteoporosis (WHO definition) HR (95% CI) ^a , N = 3,246	No severe osteoporosis HR (95% CI) ^a , N = 3,119
Morphometric vertebral fracture	0.65 (0.56, 0.76)	0.47 (0.35, 0.63)
Clinical vertebral fractures	0.77 (0.62, 0.95)	0.76 (0.50, 1.16)
Any clinical fracture ^b	0.85 (0.73, 0.98)	0.79 (0.64, 0.98)
Any clinical osteoporotic fracture ^b	0.84 (0.72, 0.98)	0.76 (0.61, 0.94)
Hip fracture	1.14 (0.76, 1.70)	0.78 (0.49, 1.23)
Outcome	Severe osteoporosis (FRAX definition) HR (95% CI) ^a , N = 4,137	No severe osteoporosis HR (95% CI) ^a , N = 2,131
Morphometric vertebral fracture	0.63 (0.54, 0.74)	0.50 (0.37, 0.67)
Clinical vertebral fractures	0.77 (0.62, 0.95)	0.72 (0.47, 1.10)
Any clinical fracture ^b	0.84 (0.73, 0.96)	0.79 (0.62, 1.01)
Any clinical osteoporotic fracture ^b	0.83 (0.72, 0.96)	0.74 (0.57, 0.95)
Hip fracture	0.94 (0.67, 1.32)	0.99 (0.48, 2.03)

Abbreviations: CI, confidence interval; HR, hazard ratio.

Values in bold represent statistically significant differences observed between treatment groups.

^a Hazard ratios for the meta-analysed results are based on an adjusted Poisson regression model.

^b Includes both vertebral and non-vertebral fractures.

WHO definition: Patients with a BMD T-score -2.5 and a prior fragility fracture.

FRAX definition: Patients with a 10-year probability of fracture greater than that of a patient with a BMD T-score -2.5 and a prior fragility fracture. Source: Table C-4 (p 79), Table C-5 (p 79), Table C-6 (p 79) of the submission

- 6.17 There were no statistically significant differences in fracture outcomes associated with disease severity (interaction test, $p > 0.30$) or the presence/absence of cardiovascular risk factors (interaction test, $p > 0.30$).

Table 5: Subgroup analyses of risk of major osteoporotic fracture^a based on BMD levels in patients with severe osteoporosis

Risk percentile ^b	10-year fracture risk	Severe osteoporosis (WHO definition) HR (95% CI) ^c , N = 3,246	Severe osteoporosis (FRAX definition) HR (95% CI) ^c , N = 4,137
10 th	8.4%	0.69 (0.58, 0.84)	0.71 (0.59, 0.85)
25 th	11.5%	0.72 (0.61, 0.85)	0.73 (0.62, 0.86)
50 th	16.1%	0.76 (0.67, 0.87)	0.76 (0.67, 0.87)
75 th	22.5%	0.82 (0.72, 0.94)	0.81 (0.72, 0.92)
90 th	30.2%	0.90 (0.77, 1.06)	0.88 (0.75, 1.03)

Abbreviations: BMD, bone mineral density; CI, confidence interval; HR, hazard ratio

Values in bold represent statistically significant differences observed between subgroups.

^a The definition of a major osteoporotic fracture was unclear in the sponsor's response. In the individual trials a major fracture was defined as clinical vertebral, hip area, proximal femur, ribs-sternum, pelvic-sacrum, forearm, wrist or shoulder fracture

^b Based on baseline BMD levels

^c Hazard ratios for the meta-analysed results are based on an adjusted Poisson regression model

WHO definition: Patients with a BMD T-score < -2.5 and a prior fragility fracture

FRAX definition: Patients with a 10-year probability of fracture greater than that of a patient with a BMD T-score < -2.5 and a prior fragility fracture

Source: Table 6 (p 9) of the sponsor's response to EMA assessment report

- 6.18 There was a potential interaction between treatment effect and underlying risk of fracture, with smaller treatment effects observed in patients with higher risk. The interaction test was statistically significant in severe patients using the WHO definition ($p = 0.033$) but not the FRAX definition ($p = 0.076$).
- 6.19 The results of the indirect comparison of strontium ranelate vs. denosumab are presented in the following table.

Table 6: Indirect comparison of fracture outcomes with strontium ranelate vs. denosumab using a placebo common comparator

Trial	Strontium ranelate	Placebo	Denosumab	Relative risk (95% CI)
Morphometric vertebral fractures, n/N (%)				
SOTI/TROPOS (N = 5,082)	339/2536 (13.4%)	543/2546 (21.3%)	-	0.63 (0.56, 0.71)
FREEDOM (N = 7,393)	-	264/3691 (7.2%)	86/3702 (2.3%)	0.32 (0.26; 0.41)
Indirect estimate of effect (results < 1 favour strontium ranelate)				1.97 (1.52; 2.55)
Clinical vertebral fractures, n/N (%)				
SOTI/TROPOS (N = 5,082)	194/2536 (7.6%)	255/2546 (10.0%)	-	0.75 (0.56, 1.00)
FREEDOM (N = 7,808)	-	92/3906 (2.4%)	29/3902 (0.7%)	0.32 (0.21; 0.48)
Indirect estimate of effect (results < 1 favour strontium ranelate)				2.34 (1.42, 3.88)
Non-vertebral fractures, n/N (%)				
SOTI/TROPOS (N = 6,374)	345/3198 (10.8%)	398/3176 (12.5%)	-	0.86 (0.75, 0.99)
FREEDOM (N = 7,808)	-	293/3906 (7.5%)	238/3902 (6.1%)	0.81 (0.69; 0.96)
Indirect estimate of effect (results < 1 favour strontium ranelate)				1.06 (0.86; 1.32)
Hip fractures, n/N (%)				
TROPOS (N = 4,932)	62/2479 (2.5%)	74/2453 (3.0%)	-	0.83 (0.59, 1.16)
FREEDOM (N = 7,808)	-	43/3906 (1.1%)	26/3902 (0.7%)	0.61 (0.37; 0.98)
Indirect estimate of effect (results < 1 favour strontium ranelate)				1.36 (0.75, 2.46)

Abbreviations: CI, confidence interval. **Values in bold represent statistically significant differences observed between groups.** Source: Table B-49 (p 63) of the submission

- 6.20 Treatment with denosumab was associated with statistically significant reductions in morphometric and clinical vertebral fracture risk compared to strontium ranelate. There was no difference in non-vertebral fracture or hip fracture risk between treatments.
- 6.21 There were substantial differences in placebo event rates between trials indicating that the trials may not have been sufficiently exchangeable to justify their use in an indirect comparison.
- 6.22 The ESC noted that there were no data for the subgroup eligible for strontium ranelate on the PBS and it was unclear whether these patients would have the same response as those in the trials.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Comparative harms

6.23 A direct comparison of strontium ranelate vs. placebo is presented in the following table.

Table 7: Overall summary of adverse events reported in strontium ranelate trials

	SOTI 3-year		TROPOS 5-year		MALEO 2-year	
	Strontium N = 826	Placebo N = 814	Strontium N = 2,526	Placebo N = 2,503	Strontium N = 173	Placebo N = 187
Proportion of patients with adverse events emergent under treatment, n/N (%)						
Any events	730 (88.4%)	711 (87.3%)	2311 (91.5%)	2295 (91.7%)	153 (88.4%)	84 (96.6%)
- Nausea	41 (5.0%)	31 (3.8%)	196 (7.8%)	120 (4.8%)	NR	NR
- Diarrhoea	50 (6.1%)	29 (3.6%)	182 (7.2%)	136 (5.4%)	NR	NR
- Thromboembolism	21 (2.5%)	12 (1.5%)	(2.7%)	(2.1%)	3 (1.7%)	0 (0.0%)
- Myocardial infarction	4 (0.5%)	6 (0.7%)	52 (2.1%)	29 (1.2%)	NR	NR
- Hypercholesterolemia	61 (7.4%)	44 (5.4%)	184 (7.3%)	134 (5.4%)	NR	NR
- Disturbance of consciousness	16 (1.9%)	14 (1.7%)	71 (2.8%)	54 (2.2%)	NR	NR
- Seizures	2 (0.2%)	0 (0.0%)	10 (0.4%)	2 (0.1%)	NR	NR
- Memory loss	12 (1.5%)	6 (0.7%)	70 (2.8%)	59 (2.4%)	NR	NR
- Headache	15 (1.8%)	19 (2.3%)	92 (3.6%)	68 (2.7%)	NR	NR
- Dermatitis	17 (2.1%)	13 (1.6%)	59 (2.3%)	50 (2.0%)	NR	NR
- Eczema	8 (1.0%)	10 (1.2%)	51 (2.0%)	37 (1.5%)	NR	NR
Serious adverse events	188 (22.8%)	188 (23.1%)	781 (30.9%)	751 (30.0%)	51 (29.5%)	26 (29.9%)
Treatment-related events	169 (20.5%)	135 (16.6%)	575 (22.8%)	420 (16.8%)	50 (28.9%)	26 (29.9%)
Discontinuations due to adverse events	168 (20.3%)	121 (14.7%)	738 (29.2%)	663 (26.5%)	31 (17.9%)	12 (13.8%)
Deaths	29 (3.5%)	21 (2.6%)	227 (9.0%)	229 (9.1%)	3 (1.7%)	1 (0.5%)

Source: Table B-51 (p 64) of the submission; 3-year SOTI trial report; 5-year TROPOS trial report; Kaufmann (2013) publication

- 6.24 Strontium ranelate was associated with a higher incidence of treatment-related events and discontinuations due to adverse events compared with placebo. Adverse events more frequently reported with strontium ranelate included gastrointestinal disorders (nausea, diarrhoea), nervous system disorders (headache, disturbances of consciousness, seizures, memory loss), skin disorders (dermatitis, eczema) hypercholesterolemia, myocardial infarction, thromboembolism and transient increases in blood creatinine phosphokinase laboratory measures.
- 6.25 Long-term (10-year) treatment with strontium ranelate was not associated with any additional safety signals.
- 6.26 To address the risk of myocardial infarction and venous thromboembolism, the submission presented additional retrospective subgroup analyses (see Table 8) suggesting that these risks may be at least partially mitigated by restricting treatment to patients without cardiovascular complications (consistent with the current product information). The subgroup analyses may not have been adequately powered to detect a meaningful difference in risk between treatments.

Table 8: Risk of serious cardiac disorders and thromboembolism with strontium ranelate compared to placebo

	Serious cardiac events		Myocardial infarction		Thromboembolism	
	Strontium	Placebo	Strontium	Placebo	Strontium	Placebo
Whole post-menopausal osteoporosis population						
Number of patients	3803	3769	3803	3769	3803	3769
Incidence, n (%)	262 (6.9%)	215 (5.7%)	64 (1.7%)	40 (1.1%)	71 (1.9%)	47 (1.2%)
Rate per 1000 patient years	23.2	19.1	5.7	3.6	6.3	4.2
Odds ratio (95% CI)	1.22 (1.02, 1.48)		1.60 (1.07, 2.38)		1.51 (1.04, 2.19)	
Whole post-menopausal osteoporosis population without cardiovascular contraindications						
Number of patients	2035	2005	2035	2005	2035	2005
Incidence, n (%)	83 (4.1%)	73 (3.6%)	15 (0.7%)	15 (0.7%)	32 (1.6%)	26 (1.3%)
Rate per 1000 patient years	14.2	12.5	2.6	2.6	5.5	4.5
Odds ratio (95% CI)	1.13 (0.82, 1.57)		0.99 (0.48, 2.04)		1.22 (0.73, 2.06)	
Severe post-menopausal osteoporosis population without cardiovascular contraindications (WHO definition)						
Number of patients	975	977	975	977	975	977
Incidence, n (%)	42 (4.3%)	40 (4.1%)	5 (0.5%)	6 (0.6%)	17 (1.7%)	16 (1.6%)
Rate per 1000 patient years	14.4	13.8	1.7	2.1	5.8	5.5
Odds ratio (95% CI)	1.05 (0.67, 1.64)		0.86 (0.26, 2.86)		1.05 (0.53, 2.10)	
Severe post-menopausal osteoporosis population without cardiovascular contraindications (FRAX definition)						
Number of patients	1243	1259	1243	1259	1243	1259
Incidence, n (%)	59 (4.7%)	49 (3.9%)	12 (1.0%)	11 (0.9%)	19 (1.5%)	16 (1.3%)
Rate per 1000 patient years	16.5	13.7	3.4	3.1	5.3	4.5
Odds ratio (95% CI)	1.22 (0.82, 1.79)		1.10 (0.48, 2.52)		1.18 (0.60, 2.31)	
Severe post-menopausal osteoporosis population without cardiovascular contraindications (PSUR, definition unclear)						
Number of patients	1237	1184	1237	1184	1237	1184
Incidence, n (%)	52 (4.2%)	46 (3.9%)	7 (0.6%)	8 (0.7%)	29 (2.3%)	22 (1.9%)
Rate per 1000 patient years	14.1	13.1	1.9	2.3	7.8	6.3
Odds ratio (95% CI)	1.09 (0.73, 1.64)		0.85 (0.31, 2.37)		1.29 (0.74, 2.25)	

Abbreviations: CI, confidence interval; NR, not reported.

Values in bold represent statistically significant differences observed between groups.

Source: Table C-7 (p 80) of the submission; Table 2 (p 21) and Table 3 (p 22) of the 2014 strontium ranelate EMA assessment report

For more detail on PBAC's view, see section 7 "PBAC outcome"

Benefits/harms

- 6.27 A summary of the comparative benefits and harms for strontium ranelate versus placebo is presented in the table below for the overall trial populations. Absolute differences in fracture outcomes in the more-relevant severe disease subgroups could not be estimated from the limited information available.

Table 9: Summary of comparative benefits and harms for strontium ranelate and placebo

Benefits						
Outcome	Strontium	Placebo	HR (95% CI)	Crude incidence per 100 patients over 3 years		RD (95% CI)
				Strontium	Placebo	
New morphometric vertebral fractures						
Meta-analysis (SOTI/ TROPOS 3 yrs)	341/2536	543/2546	0.60 (0.52, 0.69)	13.4	21.3	-0.09 (-0.13, -0.04)
New clinical vertebral fractures						
Meta-analysis (SOTI/ TROPOS 3 years)	194/2536	255/2546	0.75 (0.62, 0.92)	7.6	10.0	-0.03 (-0.08, 0.02)
New clinical non-vertebral fractures						
Meta-analysis (SOTI/ TROPOS 3 years)	345/3198	398/3176	0.84 (0.72, 0.98)	10.8	12.5	-0.02 (-0.03, -0.00)
New clinical hip fractures (proximal femur fractures)						
TROPOS (3 years)	62/2479	74/2453	0.85 (0.61, 1.19)	2.5	3.0	-0.01 (-0.01, 0.00)
Harms						
Outcome	Strontium	Placebo	RR (95% CI)	Crude incidence per 100 patients over 3 years		RD (95% CI)
				Strontium	Placebo	
Treatment-related adverse event						
Meta-analysis (SOTI/ TROPOS 3 years)	732/3352	575/3317	1.27 (1.15, 1.40)	21.8	17.2	0.05 (0.03, 0.07)

Abbreviations: CI, confidence interval; HR, hazard ratio; RD, risk difference; RR, relative risk
Source: Constructed during the evaluation

- 6.28 On the basis of meta-analysis presented in the submission, for every 100 patients treated with strontium ranelate in comparison to placebo:
- Approximately 9 fewer patients would have a new morphometric vertebral fracture (i.e. detectable on x-ray or other imaging but not necessarily clinically apparent) over 3 years
 - Approximately 3 fewer patients would have a new clinical vertebral fracture over 3 years (although the ESC noted that the statistical significance of this result was borderline)
 - Approximately 2 fewer patients would have a new clinical non-vertebral fracture over 3 years
 - There would be no difference in the number of patients with a new hip fracture over 3 years
 - Approximately 5 additional patients would experience a treatment-related adverse event over 3 years
- 6.29 No benefits and harms comparison was presented for strontium ranelate versus denosumab as clinical results indicated inferiority of strontium ranelate.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Clinical claim

- 6.30 The submission described strontium ranelate as superior in terms of efficacy and inferior in terms of safety compared to placebo. This claim may be reasonable. However, the ESC noted that strontium ranelate is associated with relatively small

reductions in morphometric and clinical vertebral and non-vertebral fractures and no reduction in hip fractures. Furthermore, the ESC considered that the submission did not demonstrate effectiveness in the proposed PBS population.

- 6.31 The submission described strontium ranelate as inferior in terms of efficacy and inferior in terms of safety compared with denosumab. The ESC considered this claim was reasonable.
- 6.32 The PBAC considered that the claim of superior comparative effectiveness compared with placebo may be reasonable and that the claim of inferior comparative safety compared with placebo was reasonable.
- 6.33 The PBAC considered that the claim of inferior comparative effectiveness and safety compared with denosumab was reasonable.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

Economic analysis

- 6.34 The submission presented a modelled economic analysis assessing the cost-effectiveness of strontium versus best supportive care for patients with severe established osteoporosis at high risk of fracture who are unable to use other osteoporosis medications (i.e. last-line treatment). The PSCR argued that the economic analysis was clearly relevant for this subgroup of patients.
- 6.35 No economic analysis was presented for patients using strontium ranelate as a ‘second-line’ treatment (i.e. patients with other treatment options). The submission claimed that strontium ranelate is inferior to denosumab and patients who can use denosumab should use denosumab in preference to strontium ranelate. The PSCR agreed that the economic analysis was probably not relevant to the sub-group of patients currently receiving strontium who could potentially switch to another therapy. In this regard, the ESC noted that this subgroup was potentially a large proportion of the patients currently being treated with strontium. The PSCR argued that constructing an economic evaluation for this subgroup of patients would be inherently challenging given the available clinical data.

Table 10: Summary of model structure and rationale

Time horizon	10 years
Outcomes	Quality-adjusted life years, fractures, life years
Methods used to generate results	Markov cohort expected value analysis
Health states	Prior fracture, hip fracture (5-year tunnel state), vertebral fracture (5-year tunnel state), other non-vertebral fracture (5-year tunnel state), myocardial infarction (1-cycle transition state), venous thromboembolism (1-cycle transition state), death
Cycle length	6 months; half-cycle corrections applied
Transition probabilities	Baseline fracture risks and standardised mortality rates from the Dubbo Osteoporosis study. Fractures risk adjusted for treatment efficacy based on subgroup results. Adverse event risks based on subgroup results.
Discount rate	5% for costs and outcomes
Software package	TreeAge Pro 2014

Source: constructed during the evaluation

- 6.36 During the evaluation three errors were identified in the TreeAge model relating to patient age, serious adverse event disutilities and chronic fracture costs. Estimates calculated during the evaluation were corrected for these errors (see Table 10). The errors had a substantial impact on the economic model. The PSCR acknowledged these errors and agreed with the corrections made during the evaluation.
- 6.37 The key drivers of the model were the treatment efficacy estimates and the assumption of a fixed recovery period of five years for all fractures (which appeared excessive for many osteoporotic fractures and strongly favoured strontium). The PSCR acknowledged that five years may not have been an appropriate base case assumption and reduced this period to three years in a revised base case (see paragraph 6.44).
- 6.38 Other important issues with the model included:
- The inappropriate use of non-statistically significant differences in hip fracture (favoured strontium), myocardial infarction (favoured strontium) and venous thromboembolism (favoured best supportive care). The PSCR acknowledged the inclusion of these point estimates in the model was contestable but argued that the lack of statistical significance was a reflection of the low power of the clinical trials for these particular outcomes, rather than absence of a true effect of therapy. The ESC considered that the use of non-statistically significant different point estimates for these outcomes in the model was inappropriate and noted that the PSCR presented a revised base case that excluded these non-significant treatment effects (see paragraph 6.44)
 - The use of 'any clinical fracture' (which included both vertebral and non-vertebral fractures) to proxy for non-vertebral fractures (which favoured strontium due to the larger treatment effect in vertebral fractures). The PSCR acknowledged that while this was less than ideal, the impact on the evaluation results was marginal because the relative risk estimate employed for the severe osteoporosis population (0.83: 0.72-0.96) was not significantly different from that reported specifically for non-vertebral osteoporotic fractures in the overall SOTI/TROPOS population (0.84: 0.72-0.98).
 - The uncertainty associated with fracture utility values given the substantial heterogeneity in published values for different fracture health states. The PSCR argued that the uncertainty was an inherent property of the available literature, that the utility values were not directly comparable, and that the values were the best available estimates of the health related quality of life impact of osteoporosis. The ESC noted that SF-36, which was administered every six months in the SOTI and TROPOS trials, could have been used to derive trial based SF-6D utilities but was not used in the submission.
 - The uncertainty associated with baseline fracture risk which varied substantially based on BMD levels in patients with a prior fragility fracture.
 - The assumption that all patients with acute fracture are hospitalised was not consistent with available data and favoured strontium. Recent health resource data for Australian osteoporosis patients supported this assumption for hip fractures but indicated that only 67% of vertebral fractures, 63% of wrist fractures and 72% of other fractures in women 70 years of age or older required hospitalisation. The corresponding numbers for male patients were 50% for vertebral fractures, 50% for wrist fractures and 67% for other fractures (Osteoporosis Australia: Burden of Disease Analysis 2012-2022).

- The ESC considered that the clinical validity of the structural assumption that people return to baseline risk of fracture after exiting fracture tunnel states was unclear. However, the ESC considered that this assumption was unlikely to favour strontium.

6.39 The evaluation considered that real-world treatment adherence (both compliance and persistence) was likely to be substantially lower than estimated in the modelled population but the impact on the economic analysis could not be adequately explored due to the structural limitations of the model design. The submission and PSCR claimed that this was a conservative assumption as it did not account for the potential for residual treatment effects after therapy discontinuation (which would improve health outcomes without increasing costs); conversely, patients may discontinue therapy before gaining sufficient exposure to achieve claimed treatment effects (which would increase costs without improving outcomes).

6.40 The results of the modelled economic evaluation in the submission are summarised in the table below.

Table 11: Results of the modelled economic evaluation (assuming 5 year fracture recovery period)

	Strontium	Best supportive care	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	<i>5.3539</i>	<i>5.2985</i>	<i>0.0554</i>
Incremental cost per QALY gained			\$ [REDACTED]

Note: Figures in italics were corrected during the evaluation to account for the errors discussed in paragraph 6.36.

6.41 Based on the corrected economic model, treatment with strontium ranelate was associated with costs per QALY of \$45,000 – \$75,000 compared to best supportive care (the original uncorrected estimate was \$15,000 - \$45,000). Alternatively, the submission expressed the ICER as savings of \$45,000 – \$75,000 per QALY foregone in the case that strontium ranelate is delisted from the PBS.

6.42 The PSCR argued that it was inappropriate for the commentary to invert the economic evaluation to assess the cost-effectiveness of strontium ranelate for its current listing rather than the cost-effectiveness of delisting. The submission claimed that assessing the cost-effectiveness of delisting better reflects the current context for decision-making. However, the ESC considered that the economic evaluation did not account for the majority of patients currently treated with strontium ranelate and therefore did not adequately reflect the cost-effectiveness of delisting (which would affect all patients, not just the subgroup of new initiating patients using strontium ranelate as last-line therapy). Therefore the analysis was inverted during the evaluation to assess the cost-effectiveness of the intent of the current listing which is more consistent with the presented data and is easier to interpret for decision-making purposes.

6.43 The results of the univariate sensitivity analyses indicated that the economic model was most sensitive to treatment efficacy estimates for vertebral fracture, assumed duration of the recovery period and baseline fracture risk. Other sensitive variables included the time horizon, treatment efficacy estimates for other non-vertebral fracture, fracture utility values and acute fracture costs.

- 6.44 The PSCR proposed a revised base case which: corrected for the identified programming errors; excluded statistically non-significant treatment effects; decreased the assumed average fracture recovery period to three years; and reduced the dispensed price of strontium by █%, to \$█. The revised base case ICER increased to \$45,000 – \$75,000 per QALY.
- 6.45 The pre-PBAC response proposed a further revision to the base case, which included all the changes outlined above and a █% reduction in the dispensed price of strontium (to \$█). These changes resulted in a revised base case ICER of \$45,000 – \$75,000 per QALY.

Table 12: Revised base case economic analysis

Analysis	ICER
Submission base case	\$█
Corrected for programming errors	\$█
Excluding non-significant effects	\$█
Fracture recovery period of 3 years	\$█
█% price reduction to \$█ DPMQ	\$█
Further █% price reduction to \$█ DPMQ (revised base case)	\$█

Source: Pre-PBAC Response (p.4)

- 6.46 The PBAC considered that if the submission was seeking PBS-listing of strontium ranelate, it would not consider an ICER of around \$45,000 – \$75,000 per QALY sufficiently cost effective for this indication. Accordingly, as the submission is seeking continued listing of strontium ranelate, the PBAC considered that a pragmatic approach would be to recommend continued listing of strontium on the condition that the price of strontium is reduced such that the ICER would be less than \$15,000 - \$45,000 per QALY. An ICER of less than \$15,000 - \$45,000 per QALY would be broadly in line with previous PBAC considerations of drugs for this indication and in line with the ICER that the submission had initially proposed.

For more detail on PBAC’s view, see section 7 “PBAC outcome

Drug cost/patient/year: \$█

- 6.47 The annual cost of strontium ranelate and other PBS-listed osteoporosis medications, based on the indicated number of scripts per year, are summarised in the table below. With a reduced requested DPMQ (from the pre-PBAC response) of \$█ and assuming 13 scripts per year, the annual cost of strontium ranelate is \$█. By comparison, the annual cost of strontium at the current DPMQ of \$52.00 was \$676.

Table 13: Annual drug costs for PBS-listed osteoporosis medications

Treatment	Annual cost (DPMQ)
Strontium ranelate	\$ [REDACTED] (13 scripts)
Alendronate monotherapy	\$194 (13 scripts)
Alendronate fixed dose combinations	\$592 (13 scripts)
Risedronate monotherapy	\$536-\$547, depending on formulation (13 scripts)
Risedronate fixed dose combinations	\$594 (13 scripts)
Zoledronic acid	\$590 (1 script)
Denosumab	\$592 (2 scripts)
Raloxifene	\$657 (13 scripts)
Teriparatide	\$5,703 (13 scripts)

Estimated PBS usage & financial implications

- 6.48 This submission was not considered by DUSC. However, in response to a request from the PBAC, the DUSC Secretariat provided an analysis of dispensing data to assess the proportion of patients currently taking strontium who may have contraindications or precautions to use of strontium as inferred from co-administered medicines. The analysis concluded the following: *Despite a declining trend in the number of prevalent and incident strontium patients, the extent of co-administration of medicines that may infer a contraindication or precaution to the use of strontium does not appear to have changed to any great extent based on the comparison of February 2014 and February 2015 PBS data. Caution is required in interpreting the result.* The pre-PBAC response noted a number of serious limitations to the analysis which called into question both these results and the conclusions drawn from them.
- 6.49 The submission used a market share approach to estimate the utilisation and financial implications associated with continued listing or delisting strontium ranelate from the PBS.

Table 14: Estimated utilisation of strontium ranelate and cost to the PBS over the next five years of listing

	Year 1 (2015)	Year 2 (2016)	Year 3 (2017)	Year 4 (2018)	Year 5 (2019)
Continued listing scenario					
Treated patients	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated strontium scripts	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total cost less co-payments	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Delisting scenario					
Patients previously treated with strontium	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
- Discontinuing therapy (65.7%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
- Treated with alendronate (4.5%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
- Treated with risedronate (5.9%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
- Treated with zoledronic acid (0.7%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
- Treated with denosumab (22.3%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
- Treated with raloxifene (0.8%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
- Treated with teriparatide (0.2%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total cost (DPMQ) less co-payments	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Difference between scenarios					
Total cost of strontium ranelate	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Total cost other therapies	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to the PBS	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]

Abbreviations: DPMQ, dispensed price per maximum quantity; PBS, Pharmaceutical Benefits Scheme

- 6.50 The above redacted table shows that if strontium ranelate continued to be listed on the PBS, at year 5 the estimated number of patients would be less than 10,000 (down from less than 10,000 in year 1) and the cost to the PBS would be less than \$10 million (down from less than \$10 million in year 1).
- 6.51 The estimated financial implications of either continued listing or delisting were highly uncertain due to methodological issues with calculating patient numbers from scripts, limited current data to inform discontinuation rates, and the assumption that discontinuation patterns observed with strontium ranelate available on the PBS would be reflective of switching patterns if strontium ranelate was removed from the PBS.
- 6.52 The PSCR stated that the sponsor did not necessarily agree with the issues raised during the evaluation regarding the utilisation and financial estimates, but was generally prepared to concede given their likely marginal impact on the decision context.

For more detail on PBAC's view, see section 7 "PBAC outcome"

7 PBAC Outcome

- 7.1 The PBAC recommended that strontium ranelate should remain listed on the PBS for the treatment of severe established osteoporosis in patients unable to use other osteoporosis medications and without cardiovascular contraindications.
- 7.2 The PBAC recalled that in April 2014, the TGA issued an alert warning against use of the drug in patients with cardiovascular contraindications and restricting use to patients unable to take other osteoporosis medications. As a result, the PBAC recommended changes to the strontium ranelate restriction at its July 2014 meeting and noted that it was of a mind to recommend delisting of strontium from the PBS. However, the PBAC considered that it would be appropriate for the sponsor to have the opportunity to establish the cost-effectiveness of strontium ranelate in patients with severe established osteoporosis unable to use other treatments due to contraindication or intolerance.
- 7.3 The PBAC noted advice from Osteoporosis Australia and expert advice provided with submission (from the Institute of Bone and Joint Research and Menzies Research Institute) which indicated that strontium ranelate has a clinical role in the treatment of osteoporosis in patients intolerant to other osteoporosis drugs and without cardiovascular contraindications. The PBAC accepted this clinical place for strontium ranelate and considered that the number of patients currently taking strontium ranelate who could potentially use another agent will decline over time.
- 7.4 The PBAC agreed with the additional clinical criterion to be included in the restriction suggested in the PSCR: *Patient must have BMD T-score \leq -2.5*. The PBAC also recommended that the note suggested in the pre-PBAC response be included in the prescriber instructions: *Patients should be evaluated for cardiovascular risk prior to commencement of strontium ranelate and during ongoing treatment on a regular basis generally every 6 months. See Product Information for further details.*

- 7.5 The PBAC considered that best supportive care was the appropriate comparator for last line use of strontium ranelate (i.e. for patients that are intolerant or contraindicated to other osteoporosis medications).
- 7.6 The PBAC noted the statistically significant difference in morphometric vertebral fractures in both the SOTI and TROPOS trials between strontium ranelate and placebo while questioning the clinical significance of the outcome. The PBAC also noted that strontium ranelate was associated with reductions in clinical vertebral fractures and non-vertebral fractures compared with placebo, although these estimates appeared more uncertain due to inconsistency between trials and borderline statistical significance of some results. While noting the lack of a statistically significant difference in clinical hip fractures between placebo and strontium ranelate, the PBAC noted that a very large study would be required to demonstrate a significant difference in some fractures. Overall, the PBAC considered that the claim of superior comparative effectiveness compared with placebo may be reasonable.
- 7.7 The PBAC noted that the retrospective subgroup analyses presented in the submission suggested that the risk of serious cardiac events, myocardial infarction and thromboembolism could be at least partly mitigated by restricting treatment to patients without cardiovascular complications (consistent with the current restriction and product information). However, the PBAC noted that these analyses may not have been adequately powered to detect a meaningful difference between treatments. Overall, the PBAC considered that the claim of inferior comparative safety compared with placebo was reasonable. The PBAC considered that the risk of cardiovascular related adverse events would be reduced if strontium ranelate were only used to treat patients with no other options and without cardiovascular contraindications.
- 7.8 The PBAC noted that the model provided in the submission included a number of errors and inappropriate assumptions, as identified by the ESC (see paragraphs 6.36-6.38). A revised model was presented in the PSCR that resulted in a significantly higher ICER per QALY. Following a subsequent reduction in the price, the ICER presented in the pre-PBAC response was around \$45,000 - \$75,000 per QALY.
- 7.9 The PBAC noted the additional analysis from the DUSC Secretariat of the number and proportion of patients with cardiovascular contraindications who are continuing to take strontium ranelate. The PBAC considered this analysis had a number of caveats, as outlined in the analysis, which limited the interpretation of the results. The PBAC noted that the analysis demonstrated the declining trend in the number of incident and prevalent patients taking strontium ranelate and that the current market share is lower than █%. In this regard, the PBAC considered that current utilisation of strontium ranelate is relatively small compared with the overall osteoporosis drug market and will continue to decline over time.
- 7.10 The PBAC noted that strontium ranelate is currently not available to be prescribed by nurse practitioners and advised that this was appropriate.
- 7.11 The PBAC noted that the Safety Net 20 Day Rule currently applies to this listing.

Outcome:
Recommended

8 Recommended listing

8.1 Amend existing listing as follows:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
STRONTIUM RANELATE 2g granules	28	5	Protos®	Servier Laboratories
Restriction	Section 85 (General Schedule) Authority Required			
Condition	Severe established osteoporosis			
Clinical criteria	Patient must have fracture due to minimal trauma, AND Patient must not receive concomitant treatment with any other PBS-subsidised anti-resorptive agent for this condition, AND Patient must be at high risk of fracture, AND Patient must have bone mineral density T-score less than or equal to -2.5, AND Patient must be unable to use other medications for the treatment of osteoporosis due to contraindications or intolerance.			
Prescriber instructions	The fracture must have been demonstrated radiologically and the year of plain x-ray or computed tomography (CT) scan or magnetic resonance imaging (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. Patients should be evaluated for cardiovascular risk prior to commencement of strontium ranelate and during ongoing treatment on a regular basis generally every 6 months. See Product Information for further details.			
Administrative advice	Note Anti-resorptive agents in established osteoporosis include alendronate sodium, risedronate sodium, denosumab, raloxifene hydrochloride, strontium ranelate and zoledronic acid.			

9 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.

10 Sponsor's Comment

The Sponsor had no comment.