

6.7 STRONTIUM RANELATE, 2g granules, 28x2 sachets, Protos[®] Servier Laboratories Australia Pty Ltd.

1 Purpose of Application

1.1 To request a change to the existing PBS listing for treatment of patients with established osteoporosis to reflect amended TGA indications following a safety review.

2 Requested listing

2.1 Strontium ranelate is currently TGA registered with the following indications:

Treatment of severe (established) osteoporosis:

- *In postmenopausal women at high risk of fracture to reduce the risk of fracture*
- *In men at increased risk of fracture.*

PROTOS should only be used when other medications for the treatment of osteoporosis are considered unsuitable (due to contraindications or intolerance).

2.2 In April 2014, the TGA issued an alert advising consumers and health professionals that Servier Laboratories (Australia) had updated the Product Information (PI) for strontium ranelate (Protos) after the completion of a TGA review. The updates to the PI, made in consultation with the TGA, emphasise the contraindications, reinforce precautions, highlight the need for regular monitoring and update data relating to the risk of adverse events.

The following black box warning was added to the PI to highlight the updated information:

PROTOS should only be used when other medications for the treatment for osteoporosis are considered unsuitable. PROTOS is contraindicated and must not be used in patients with established, current or past history of: ischaemic heart disease, peripheral vascular disease, cerebrovascular disease, uncontrolled hypertension, venous thromboembolism, pulmonary embolism. It should also not be used in patients who are temporarily or permanently immobilised. PROTOS should be used with caution in patients with risk factors for cardiovascular events or venous thrombosis: hypertension, diabetes, smoking, hyperlipidaemia. All patients prescribed PROTOS should be fully informed of the risk of cardiovascular events and venous thrombosis. Patients should be regularly monitored, every 6 months.

2.3 The sponsor did not propose revised restriction wording in line with the TGA alert.

2.4 The Department suggested the following amendments to the current listing:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
STRONTIUM Strontium ranelate 2 g granules, 28 x 2 g sachets	1	5	Protos	SE

Severity:	<i>Severe</i>
Condition:	established osteoporosis
Restriction:	Authority required (STREAMLINED)

Clinical criteria:	<p>Patient must have fracture due to minimal trauma</p> <p>AND</p> <p>Patient must not receive concomitant treatment with any other PBS-subsidised anti-resorptive agent for this condition</p> <p>AND</p> <p><i>Patient must be at high risk of fracture</i></p> <p>AND</p> <p><i>Patient must be unable to use other medications for the treatment of osteoporosis due to contraindications or intolerance</i></p>
Prescriber Instructions	<p>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.</p>
Prescriber Instructions	<p>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.</p>
Administrative Advice	<p><u>Note</u> Anti-resorptive agents in established osteoporosis include alendronate sodium, risedronate sodium, denosumab, raloxifene hydrochloride, strontium ranelate and zoledronic acid.</p>
Administrative Advice	<p><u>Note</u> <i>Continuing Therapy Only:</i> <i>For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.</i></p>

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

3 Background

- 3.1 Strontium has been PBS-listed since 1 April 2007.
- 3.2 At its July 2005 meeting, the PBAC recommended the listing of strontium as the sole-PBS subsidised antiresorptive agent for treatment of established post-menopausal osteoporosis in patients with fracture due to minimal trauma. Listing was recommended on a cost-minimisation basis with alendronate for the outcome of morphometric vertebral fracture. The equi-effective doses were strontium 2 g daily and alendronate 70 mg weekly.
- 3.3 Following this recommendation, the PBAC subsequently considered strontium on the following occasions:
- March 2006: the sponsor requested a change to the recommended basis of listing for strontium from cost-minimisation to cost-effectiveness. The PBAC rejected the submission.

- November 2006: the submission requested a listing for the prevention of fractures due to osteoporosis in postmenopausal women who have a contraindication or an intolerance to alendronate. The PBAC rejected the submission because of uncertain clinical benefit and unacceptable cost-effectiveness.
- November 2006: the submission requested a listing for the prevention of fractures due to osteoporosis in postmenopausal women. The PBAC rejected the submission.
- March 2007: the minor submission requested an extension to the listing to include women aged 70 years or older with low bone mineral density (BMD) T-score of -3.0 or less and without prevalent fracture. The PBAC deferred to allow analysis of the submission by the Pharmaceutical Evaluation Section and consideration by the ESC.
- July 2007 meeting: Following its deferral in March 2007 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.
- July 2012: the submission requested amendment of 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 PBAC recommended amending the listing.
- November 2012: the submission requested revision of the relative weightings of alendronate sodium and risedronate sodium as the basis for calculating the price of strontium. The PBAC recommended that the weighted proportions as presented in the submission form the basis for calculating the price of strontium in this indication.

- 3.4 On 1 August 2013, the PBS listing for strontium was amended to remove the primary prevention indication following an amendment to the TGA approved indications.

4 Clinical place for the proposed therapy

- 4.1 The amended TGA approved indication for strontium effectively positions it as a second line treatment option, for a sub-group of patients with severe disease and at high risk of fracture, after failure of or inability to use first line treatments.

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

5 Comparator

- 5.1 The sponsor did not nominate a comparator.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 As a minor submission, there was no hearing for this item.

Consumer comments

- 6.2 No consumer comments were received for this item.

Clinical trials

6.3 The minor submission did not present any clinical data

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Comparative effectiveness

6.4 The minor submission did not present any clinical data.

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Comparative harms

6.5 The minor submission did not present any clinical data.

Benefits/harms

6.6 The minor submission did not present any clinical data.

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

Clinical claim

6.7 The minor submission did not make a clinical claim.

Economic analysis

6.8 The minor submission did not present an economic analysis.

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

Estimated PBS usage & financial implications

6.9 The minor submission did not present estimates of PBS usage or financial implications of the amended listing.

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

7 PBAC Outcome

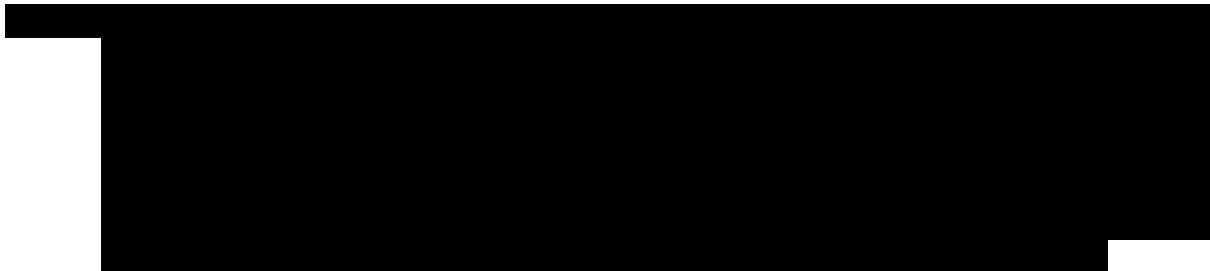
7.1 The PBAC recommended amending the listing of strontium to place it in a second line setting where the patient is unable to use other osteoporosis treatments due to contraindication or intolerance. The PBAC considered that in light of the safety concerns with strontium, returning the listing to a telephone Authority would be appropriate.

7.2 In addition to the amendments suggested by the Department, the PBAC noted the requirements for monitoring of cardiovascular and venous thromboembolism risk. The PBAC considered that this additional safety monitoring rendered the listing no longer suitable for prescribing by nurse practitioners. The PBAC therefore recommended that prescribing be limited to medical practitioners.

7.3 The PBAC noted that the cost effectiveness of strontium in a second-line setting had not been assessed and was therefore unknown. The PBAC recalled that strontium was listed on a cost-minimisation basis with alendronate, and that it had subsequently rejected a submission to change the basis of listing to cost-

effectiveness. The PBAC considered that in light of the fact that superiority of strontium over alendronate had not been accepted, and that the cost-effectiveness of strontium in a second line was unknown, there was no basis for strontium to retain its current higher price than alendronate. The PBAC therefore considered that it would be appropriate for the price of strontium to be reduced to a level equivalent with alendronate.

- 7.4 The PBAC considered that it would be appropriate for the Department to give effect to the amended listing and reduced price at the earliest opportunity. However, the PBAC acknowledged that the sponsor needed an opportunity to consider the Committee’s views and to make a submission to address the issue of the price of strontium. The PBAC noted that it may be necessary for the Department to give effect to the amended listing and the reduced price at different times.
- 7.5 The PBAC was of a mind to recommend the delisting of strontium from the PBS under the current circumstances, however noted that the sponsor had not yet had the opportunity to respond to the Committee’s concerns. The PBAC considered that it would be appropriate for the sponsor to have the opportunity to make a major submission to establish the cost-effectiveness of strontium in a second-line setting. This major submission must be considered by the Committee no later than its July 2015 meeting. Should the cost-effectiveness of strontium in second line not be established at that time, the Committee noted that it may recommend the delisting of strontium from the PBS.



- 7.6 The PBAC noted that the submission was not eligible for an Independent Review, as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Amend existing listing as follows:

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Administrative Advice	<p><u>Note</u> Anti-resorptive agents in established osteoporosis include alendronate sodium, risedronate sodium, denosumab, raloxifene hydrochloride, strontium ranelate and zoledronic acid.</p>
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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.