

5.23 ISOTRETINOIN

Capsule 5 mg,

Oratane[®], Oraderm Pharmaceuticals Pty Ltd

1 Purpose of Application

- 1.1 The minor submission requested a new Section 85 Authority Required (STREAMLINED) listing of isotretinoin 5 mg as an additional strength capsule for the treatment of severe cystic acne. The currently listed strengths are 10 mg, 20 mg and 40 mg.

2 Requested listing

- 2.1 The submission sought the same restriction as the existing PBS listed strengths of isotretinoin.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
ISOTRETINOIN Capsule 5 mg, 60	1	3	Oratane [®]	Oraderm Pharmaceuticals Pty Ltd

Category/Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Severe cystic acne
PBS Indication:	Severe cystic acne
Restriction Level/Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	The condition must be unresponsive to other therapy.
Administrative Advice	Care must be taken to comply with the provisions of State/Territory law when prescribing this drug.
Cautions	This drug causes birth defects. This drug has been reported to cause other frequent and potentially serious toxicity.

3 Background

- 3.1 Isotretinoin 5 mg was registered with the TGA on 9 February 2009 for the treatment of severe cystic acne.
- 3.2 Isotretinoin 5 mg capsule has not been previously considered by the PBAC.

3.3 Isotretinoin 10 mg and 20 mg strengths have been listed on the PBS since April 1986.

3.4 At its November 2006 meeting, the PBAC recommended isotretinoin 40 mg.

4 Population and disease

4.1 Severe cystic acne is a chronic inflammatory disease of the pilosebaceous unit resulting from androgen induced increase in sebum production, altered keratinisation, bacterial colonisation of hair follicles on the face, neck, chest and back by *Propionibacterium acnes*; and an inflammatory response in the skin.

4.2 The dosing regimen for isotretinoin is weight based and therapeutic response is dose-related, necessitating individual adjustment of dosage according to the response of the condition and the patient's tolerance of the drug. Patients commence treatment at 0.5 mg/kg per day, however the submission stated satisfactory initial responses have been reported in doses as low as 0.05 mg/kg/day.

4.3 The submission stated that patients requiring doses lower than 10 mg are dosed irregularly (2-3 times a week), rather than every day to avoid adverse events but this could lead to a suboptimal response, requiring a second course of treatment.

4.4 The submission stated that isotretinoin 5 mg capsules provides a therapeutic alternative for patients in whom a lower dose would result in a satisfactory clinical outcome, or in patients who experience dose-related adverse events on higher strength isotretinoin.

4.5 The submission also stated that 5 mg isotretinoin would be used in combination with higher strengths to provide the appropriate therapeutic dose.

5 Comparator

5.1 The minor submission nominated isotretinoin 10 mg capsule as the main comparator, assuming a 1:1 substitution of the 10 mg dose for the 5 mg dose. This may be appropriate in some patients, whereas for other patients a more appropriate comparator may be isotretinoin 10 mg 2-3 times weekly, or no treatment in patients who experienced dose-related adverse events on higher strength capsules and consequently ceased treatment.

5.2 The submission considered that isotretinoin 20 mg and 40 mg were not appropriate comparators.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item as it was a minor submission.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 As a minor submission, no clinical trials were presented in the submission.

Economic analysis

6.4 As a minor submission, there was no economic comparison presented.

Drug cost/patient/DPMQ: \$ [redacted] /month

6.5 The submission stated the pricing arrangements for the current PBS listed strengths of isotretinoin are non-linear. Therefore, the sponsor proposed an ex-manufacture price per milligram of \$ [redacted] resulting in an AEMP of \$ [redacted]. This represents a price per capsule that is [redacted] per cent lower than the 10 mg capsules, as shown in Table 1 below.

Table 1: Oratane (isotretinoin) current PBS pricing

Medicine	Capsules per pack	Total milligrams per pack	AEMP	Price per capsule	Price per mg	Percentage of price of higher strength (per capsule)
Oratane 20 mg capsule	60	1200	\$34.32	\$0.5720	\$0.0286	
Oratane 10 mg capsule	60	600	\$22.02	\$0.3670	\$0.0367	64.9%
Oratane 5 mg capsule proposed	60	300	\$ [redacted]	\$ [redacted]	\$ [redacted]	[redacted]%

Source: Table 3.1 of the submission

6.6 It may be more appropriate to cost minimise isotretinoin 5mg capsule to isotretinoin 10 mg capsule taken 2-3 times weekly as substitution may not occur 1:1 between 10 mg capsule and 5mg capsule. For a patient currently treated with 10 mg capsules 2-3 times weekly, the cost per week of treatment is \$0.73 - \$1.10. At the price currently proposed for isotretinoin 5 mg, the cost per week of treatment is \$ [redacted].

6.7 The Pre-PBAC response considered that the appropriate price for half-strength formulations is at two-thirds to 70% of the full-strength price as supported by published PBS information.

Estimated PBS usage & financial implications

6.8 The minor submission considered there would be a cost saving to the PBS because of listing isotretinoin 5 mg as patients currently prescribed the 10 mg capsule will change to the 5 mg capsule, which is less expensive, based on a 1:1 substitution rate. The submission estimated that there would be no substitution of the 20 mg and 40 mg strengths.

6.9 The assumption of 1:1 substitution may not be reasonable, specifically in the following scenarios:

- patients currently dose irregularly with 10mg capsules;
- patients who previously ceased treatment due to adverse events but would reinitiate treatment on lower strength formulation;
- patients who would complete a longer course of treatment at a lower dose to improve tolerance and outcomes; and
- where 5 mg capsules are added to existing capsule strengths to provide an appropriate therapeutic dose.

6.10 The submission claimed that the isotretinoin market was stable and the introduction of the 5 mg strength was unlikely to affect the market size. The submission assumed market growth for all isotretinoin strengths of 0.15% per year, and assumed 10% of use of the 10 mg strength of listing would be replaced with the 5 mg strength in Years 2-6.

6.11 The minor submission estimated a net save to the PBS of less than \$10 million in Year 5 of listing, with a total net save to the PBS of less than \$10 million over the first 5 years of listing. As the assumption of 1:1 substitution may not be reasonable, it is likely that the estimated net saving to the PBS is overestimated.

Table 2: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed	■	■	■	■	■	■
Estimated financial implications of isotretinoin 5 mg						
Cost to PBS/RPBS	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Copayments	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Cost to PBS/RPBS less copayments	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Estimated financial implications for isotretinoin 10 mg						
Cost to PBS/RPBS	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Copayments	-\$ ■	-\$ ■	-\$ ■	-\$ ■	-\$ ■	-\$ ■
Cost to PBS/RPBS less copayments	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Net financial implications						
Net cost to PBS/RPBS	-\$ ■	-\$ ■	-\$ ■	-\$ ■	-\$ ■	-\$ ■

Source: Minor submission, section 4 workbook.

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of a new strength of isotretinoin, in the form 5 mg capsules, for the treatment of severe cystic acne. The PBAC considered that the listing would allow for dose optimisation for patients who require a lower dose of isotretinoin than currently available.

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- 7.2 The PBAC advised that the 5 mg strength capsule would likely be used in combination with other PBS listed strengths as well as directly replacing daily or irregular dosing of the 10 mg strength capsule in some patients. As such, the utilisation and financial implications presented in the submission were most likely overestimated and estimated savings may not be realised. The PBAC considered that it would be more reasonable to remove the offset for the 10 mg form in the financial estimates due to the uncertainty of likely utilisation patterns and use of different strengths in combination.
- 7.3 The PBAC noted the standard approach to pricing half-strength formulations at two-thirds to 70% of the price of the full-strength formulation, due to the uncertain utilisation and replacement patterns. However, in this situation a price reduction for the new 5 mg strength would be appropriate to achieve price parity at a per mg level for the 5 and 10 mg strengths of the drug.
- 7.4 The PBAC noted the restriction is unchanged from the currently listed strengths of isotretinoin.
- 7.5 The PBAC advised that isotretinoin is not suitable for prescribing by nurse practitioners.
- 7.6 The PBAC recommended that the Early Supply Rule should not apply.
- 7.7 The PBAC noted that this submission was not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
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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.