**PUBLIC SUMMARY DOCUMENT**
**Product:** TREPROSTINIL SODIUM, injections, 1 mg per mL, 2.5 mg per mL, 5 mg per mL and 10 mg per mL, 20 mL multidose vial, Remodulin®
**Sponsor:** Orphan Australia Pty Ltd
**Date of PBAC Consideration:** November 2005

## 1. Purpose of Application
To seek a Section 100 listing (public and private hospital authority required benefit) for treprostinil sodium for the treatment of primary pulmonary hypertension (PPH) or pulmonary arterial hypertension (PAH) associated with connective tissue disease, in patients with disease of World Health Organisation (WHO) Functional Class III or IV severity.

## 2. Background
The PBAC has not previously considered an application for this drug.

## 3. Registration Status
Treprostinil sodium was registered by the Therapeutic Goods Authority (TGA) on 31 May 2004 and is indicated as a continuous subcutaneous infusion for the treatment of pulmonary arterial hypertension in patients with New York Heart Association (NYHA) class III-IV to diminish symptoms associated with exercise.

## 4. Listing Requested and PBAC's View
Section 100 listing:
Public and private hospital authority required benefit
Treatment of primary pulmonary arterial hypertension or pulmonary arterial hypertension associated with connective tissue disease, in patients with disease of WHO Functional Class III or IV severity.

The sponsor requested similar PBS listing and prescribing restrictions to the current listing for bosentan and iloprost.

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

## 5. Clinical Place for the Proposed Therapy
Treprostinil sodium is likely to substitute for all currently used agents including oral bosentan monohydrate, intravenous epoprostenol sodium, and inhaled iloprost trometamol.

## 6. Comparator
The PBAC accepted the submission's nomination of bosentan as the main comparator and iloprost as the secondary comparator.

## 7. Clinical Trials
The submission provided as key evidence an indirect comparison of one randomised trial of treprostinil (maximum dose 22.5 ng/kg/min; mean dose 9.37±4.9 ng/kg/min of 12 weeks duration) and one randomised trial each of bosentan (250 mg/day of 16 weeks duration) and iloprost (median 7.5 inhalations/day; 30 µg/day of 12 weeks duration), all involving placebo as the common reference.

A list of key published trials included in the submission is shown below:

| Trial/first author | Protocol title | Publication citation |
|---|---|---|
| P01:04 and P01:05 (combined results) / Simonneau G et al. | Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. | Am J Respir Crit Care Med 2002; 165:800-4. |
| Rubin LJ et al | Bosentan therapy for pulmonary arterial hypertension. | N Engl J Med 2002; 346:896-903. |
| Olschewski H et al. | Inhaled iloprost for severe pulmonary hypertension. | N Engl J Med 2002; 347:322-9. |

## 8. Results of Trials

The 'PBS sub-group' (in the treprostinil trial) consisted of those patients who matched the requested restriction: functional class III/IV with primary pulmonary hypertension (PPH), pulmonary artery hypertension (PAH) associated with connective tissue disease, exclusive of congenital heart disease (CHD), chronic thromboembolic pulmonary hypertension (CTEPH), and portopulmonary hypertension.

The results of the key trials are summarised below.

**Results of the indirect comparison – 6-minute walk test (metres)**

| Trial | Treatment | N | Median | Median diff (m) | Difference in mean (m) † | SD ** | $X^{2\ a}$ (df=1) | p-value |
|---|---|---|---|---|---|---|---|---|
| Overall Simonneau | **Treprostinil** | **232** | +10 | 16.0 (p=0.0064) | **19.7** | NR | | |
| | Placebo | **236** | 0 | | | | | |
| PBS sub-group | **Treprostinil** | 160 | +11 | 24 § (7, 41) | **32.81** | 10.8 | | |
| | Placebo | 162 | -6 | | | | | |
| Rubin | **Bosentan** | 74 | +43 * | 28.2 (p=0.0107) | **34.6** [b] | 10.8 (assumed)[d] | 0.0139 | 0.9062 |
| | Placebo | 69 | -8 | | | | | |
| Olchewski | **Iloprost** | 101 | +18 * | NR | **36.4** [c] | 10.8 (assumed)[d] | 0.0556 | 0.8137 |
| | Placebo | 102 | -19 | | | | | |

† means were calculated by assigning a value of zero rather than worst rank in the patients who died or who had their study medication stopped because of worsening symptoms of pulmonary hypertension.
* mean, not median, values reported for change from baseline in 6-minute walk test
** SD (difference – mean)
§ difference in the median change using the Hodges-Lehmann estimate which is resistant to outlying values (with a 95% CI)
[a] Chi-square value ≥5.02 is significant (i.e. a significant difference in the variable between trials)
[b] p=0.001 (compared to placebo); [c] p=0.004 (compared to placebo)
[d] No variance was provided for the difference between means, so a similar standard deviation as that observed in the treprostinil trial was assumed.

The PBAC concluded that there were no significant differences for treprostinil compared to either bosentan or iloprost in the 6-minute walk test. The distance walked in the overall treprostinil trial was lower than the distances observed in the bosentan and iloprost trials, but was similar for the treprostinil sub-group.

Survival (percent proportion of patients surviving) at > 2 year time point was 76.4% in the treprostinil PBS sub-group compared to 85.6% in the bosentan trial and 59% in the iloprost trial.

Infusion site reactions were the primary adverse events reported in the treprostinil trial. Infusion site pain was the primary reason for patient withdrawal due to adverse events, which was 7.7% in the treprostinil group and 0.4% in the placebo group. The most frequent adverse

event leading to withdrawal in the bosentan trial was abnormal hepatic function. In the iloprost trial, the total number of syncopal events in each of the treatment groups was similar, but these events were more often considered serious in the iloprost group. There was more cough and vasodilatation in the iloprost patients. Although various other adverse events occurred in patients taking each of the drugs, the PBAC noted that there were no specific trends observed suggesting differences in safety among the drugs.

## 9. Clinical Claim

The PBAC accepted the submission's claim that treprostinil was no worse than bosentan in terms of effectiveness and toxicity.

## 10. Economic Analysis

The submission presented a preliminary economic evaluation. The choice of the cost-minimisation approach was considered valid by the PBAC. The resources included were drug costs.

The equi-effective doses in the context of cost-minimisation were treprostinil 9.3 ng/kg/min (maximum dose of 40 ng/kg/min) and bosentan 125 mg twice daily (iloprost 7.5 inhalations/day @ 5.0 µg/inhalation; or 7.5 ampoules/day). This was based on the doses used in the trials.

## 11. Estimated PBS Usage and Financial Implications

The likely number of patients per year is likely to be less than 10,000 in Year 3 of listing.

The submission estimated that the financial cost per year to the PBS was less than $10 million in Year 3 of listing. The PBAC noted the overall market was not expected to grow or to grow more rapidly as a result of listing treprostinil.

## 12. Recommendation and Reasons

The PBAC recommended listing of treprostinil sodium on a cost-minimisation basis, concluding that the indirect comparison involving placebo as the common reference submitted indicated that, overall, treprostinil sodium was no worse than bosentan monohydrate. The equi-effective doses were trepostinil sodium 9.3 ng/kg/min via continuous subcutaneous infusion and bosentan 125 mg twice per day. The PBAC considered that the listing of trepostinil sodium would provide an additional treatment option to patients with a different mode of administration - that is, by subcutaneous infusion.

The PBAC considered that pricing should be based on capping the average monthly cost at the fixed monthly cost for bosentan, and should take account of the one-off cost of proving the pump to each patient.

The PBAC did not consider that the restriction for trepostinil should include a tighter continuation rule than the current bosentan and iloprost restrictions, and that capping the treprostinil cost as recommended above would limit the government's financial risk adequately.

**Recommendation:**

TREPROSTINIL SODIUM, injections, 1 mg (base) per mL, 2.5 mg (base) per mL, 5 mg (base) per mL and 10 mg (base) per mL, 20 mL multidose vial

***Restriction yet to be finalised***

| | |
|---|---|
| Restriction: | Section 100 (Highly Specialised Drugs Program)<br>Public and private hospital authority required benefit<br>Treatment of primary pulmonary arterial hypertension or pulmonary arterial hypertension associated with connective tissue disease, in patients with disease of WHO Functional Class III or IV severity. |
| Pack Size: | 1 (all strengths) |

## 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 agrees with the PBAC's recommendation. Further, the sponsor clarifies that the survival percentages quoted in Section 8 were those of patients who were not all on monotherapy. Taking into account the proportion of patients alive and on monotherapy, survival (percent proportion of patients surviving and on monotherapy) at 2 years was 81.0% in the treprostinil PBS sub-group compared to 55-70% in the bosentan trial and 18.4% in the iloprost trial.