Public Summary Document

Product:	Epoprostenol Sodium, injection set containing 1 vial powder for I.V. infusion 500 micrograms and 1 vial diluent 50 mL, injection set containing 1 vial powder for I.V. infusion 1.5 mg and 2 vials diluent 50 mL, Flolan®
Sponsor:	GlaxoSmithKline Australia Pty Ltd
Date of PBAC Consideration:	March 2006

1. Purpose of Application

This submission sought a section 100 (Highly Specialised Drug) listing on the Pharmaceutical Benefits Scheme (PBS) for the treatment of severe (Class III or IV) primary pulmonary hypertension (PPH) with the same eligibility and continuing treatment criteria as for the PPH indications of bosentan and iloprost.

Section 100 Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to prescribing through public and private hospitals which have appropriate specialist facilities.

2. Background

At the July 2004 meeting, the PBAC rejected an application for section 100 listing for epoprostenol sodium for patients with Class III or IV PPH who met certain criteria and had failed to respond to treatment with bosentan or where bosentan was contraindicated or was ceased due to intolerable adverse events, because of unacceptable cost-effectiveness.

At the March 2005 meeting, the PBAC rejected a resubmission which sought a first line section 100 listing, similar to the bosentan listing for adult and paediatric patients with Class III or IV primary pulmonary hypertension (PPH) because of uncertainty about the determination of equi-effective doses and uncertainty about the resulting cost-minimisation analysis.

3. Registration Status

Epoprostenol sodium has been designated an orphan drug by the TGA and was approved by the Therapeutic Goods Administration (TGA) on 19 September 2001 for the long-term intravenous treatment of primary pulmonary hypertension (PPH) in New York Heart Association (NYHA) functional Class III and Class IV patients.

4. Listing Requested and PBAC's View

The proposed restriction was matched word-for-word with the current bosentan PBS restriction, but only for the primary pulmonary hypertension indication. The PBAC agreed this was appropriate.

5. Clinical Place for the Proposed Therapy

Primary, or unexplained, pulmonary hypertension (PPH) is a rare lung disorder which is characterised by sustained elevations of pulmonary artery pressure without a demonstrable cause. The estimated incidence is 1-2 per million population.

The natural history of PPH is usually progressive, intractable and often fatal. Medical therapies for PPH may include anticoagulants such as warfarin, vasodilators, particularly calcium channel blockers, supportive care which may include diuretics to control fluid retention, supplemental oxygen and digoxin in some cases. Newer agents such as bosentan or epoprostenol sodium have been registered by the TGA for the treatment of more severe cases of PPH (Class III or IV) in the past few years.

6. Comparator

The submission nominated bosentan monohydrate as the main comparator. As previously, this was accepted by the PBAC.

7. Clinical Trials

The submission presented the same data as the previous March 2005 submission, an indirect comparison of the results of the pivotal studies for epoprostenol sodium (2 studies) and bosentan (2 studies) using the primary endpoint, exercise capacity measured by the 6 minute walk test, and a common reference arm, standard therapy (placebo).

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

Trial/First author	Protocol/Publication title	Publication citation
Rubin et al, (1990)	Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Results of a randomised trial.	Ann Internal Med, 1990;112:485-491.
Barst et al (1996)	Comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension.	New Engl J med 1996;334: 296-301.
Badesch et al, (2002)	Complete results of the first randomized, placebo –controlled study of bosentan, a dual endothelin receptor antagonist, in pulmonary arterial hypertension.	Curr Therapeutic Research Clinical & Experimental (2002); 63 (4): 227 – 246.
Rubin et al, (2002)	Bosentan therapy for pulmonary arterial hypertension	New Engl J Med (2002); 346 (12): 896 – 903.

The submission identified 4 new published studies which provide additional information concerning the treatment of PPH, but which do not enable any new clinical comparisons.

8. Results of Trials

There were no changes made to the trial data that was presented to the March 2005 PBAC meeting.

The key results are summarised in the table below.

(Note: the results reported in this Public Summary Document are taken from the cited publications. They may vary slightly from the numbers considered by PBAC which were taken from the sponsor's internal reports. These differences do not affect the overall conclusions).

Exercise capacity - change in distance walked in 6 minutes (metres)

Trial	N	Epoprostenol Mean	N	Placebo Mean ± SE	Incremental effect
Barst	41	40	40	-15	47
Rubin, 1990	10	132	9	87	45

Both iloprost and bosentan increased the distance walked in 6 minutes compared to placebo to a similar extent as epoprostenol.

9. Clinical Claim

The submission claimed that epoprostenol is therapeutically no worse than bosentan. The PBAC agreed with this as they had previously at the March 2005 meeting.

10. Economic Analysis

The submission presented a new cost-minimisation analysis, with new equi-effective doses.

See Recommendations and Reasons for PBAC's view.

11. Estimated PBS Usage and Financial Implications

The submission estimated the number of patients to be <10,000 by the fourth year of listing.

The cost to the PBS was estimated to be <$10 million in year 4 of listing.

12. Recommendation and Reasons

The PBAC recommended listing on a cost-minimisation basis concluding that based on the indirect comparison, epoprostenol is therapeutically no worse than bosentan. The equi-effective doses are epoprostenol, commencing at an average dose of 11.9 ng/kg per min over the first three months of treatment and escalating linearly in steps to an average dose of 27.2 ng/kg/min at 3 years, and bosentan 125 mg twice a day.

The PBAC noted that, in the trial, paediatric patients reached an average dose of 119 ng/kg/min in the third year of treatment, but noted that any such dose escalation would be factored in to a risk sharing agreement with the sponsor.

Recommendation

EPOPROSTENOL SODIUM, injection set containing 1 vial powder for I.V. infusion 500 micrograms and 1 vial diluent 50 mL and injection set containing 1 vial powder for I.V. infusion 1.5 mg and 2 vials diluent 50 mL

Restriction: Public and private hospital authority required
Application for initial PBS-subsidised treatment with epoprostenol sodium of adult patients who have not received prior PBS-subsidised treatment with either bosentan monohydrate or iloprost trometamol and who have been assessed by a physician from a designated hospital to have WHO Functional Class III primary pulmonary hypertension and a mean right atrial pressure of 8 mmHg or less, as measured by RHC, unless a RHC is contraindicated on clinical grounds.

Patients must have failed to respond [see Note for definition of response] to 6 or more weeks of appropriate vasodilator treatment unless intolerance or a contraindication to such treatment exists.

Other requirements to be consistent with those for bosentan monohydrate.

Application for initial PBS-subsidised treatment with epoprostenol sodium of adult patients who have not received prior PBS-subsidised treatment with bosentan monohydrate or iloprost trometamol and who have been assessed by a physician from a designated hospital to have:
(a) WHO Functional Class III primary pulmonary hypertension and a mean right atrial pressure greater than 8 mmHg, as measured by RHC, unless a RHC is contraindicated on clinical grounds; OR
(b) WHO Functional Class IV primary pulmonary hypertension

Other requirements to be consistent with those for bosentan monohydrate.

Application for initial PBS-subsidised treatment of patients aged less than 18 years who have been assessed by a physician from a designated hospital and who have WHO Functional Class III primary pulmonary hypertension and either a mean right atrial pressure of 8 mmHg or less, as measured by RHC, or, where a RHC cannot be performed on clinical grounds, normal right ventricular function as

assessed by ECHO.

Patients must have failed to respond [see Note for definition of response] to 6 or more weeks of appropriate prior vasodilator treatment unless intolerance or a contraindication to such treatment exists.

Other requirements to be consistent with those for bosentan monohydrate.

Application for initial PBS-subsidised treatment of patients aged less than 18 years who have been assessed by a physician from a designated hospital to have:
(a) WHO Functional Class III primary pulmonary hypertension and either a mean right atrial pressure greater than 8 mmHg, as measured by RHC, or, where a RHC cannot be performed on clinical grounds, right ventricular dysfunction as assessed by ECHO; OR
(b) WHO Functional Class IV primary pulmonary hypertension.

Other requirements to be consistent with those for bosentan monohydrate.

(swapping restriction:)
Application for initial treatment with epoprostenol sodium of adult patients with:
(a) primary pulmonary hypertension who wish to re-commence PBS-subsidised epoprostenol sodium after a break in therapy and who have demonstrated a response to their most recent course of PBS-subsidised treatment with epoprostenol sodium; OR
(b) primary pulmonary hypertension whose most recent course of PBS-subsidised treatment was with bosentan monohydrate or iloprost trometamol.

Other requirements to be consistent with those for bosentan monohydrate.

(Swapping restriction:)
Application for initial treatment with epoprostenol sodium of patients aged less than 18 years with:
(a) primary pulmonary hypertension who wish to re-commence PBS-subsidised epoprostenol sodium after a break in therapy and who have demonstrated a response to their most recent course of PBS-subsidised treatment with epoprostenol sodium; OR
(b) primary pulmonary hypertension whose most recent course of PBS-subsidised treatment was with bosentan monohydrate trometamol.

Other requirements to be consistent with those for bosentan monohydrate.

Continuing PBS-subsidised treatment with epoprostenol sodium of patients with primary pulmonary hypertension, who have received approval for initial PBS-subsidised treatment with epoprostenol sodium and have completed the initial treatment course, and who have been assessed by a physician from a designated hospital to have achieved a response to their most recent course of epoprostenol sodium treatment [see Note for definition of response].

Other requirements to be consistent with those for bosentan monohydrate.

Pack Size: 1 (both 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

No comment.