PUBLIC SUMMARY DOCUMENT
Product: Epoprostenol sodium, powder for I.V. infusion, 500 micrograms (base) with diluent, 1.5 mg (base) with diluent, Flolan®
Sponsor: GlaxoSmithKline Pty Ltd
Date of PBAC Consideration: November 2011

1. Purpose of Application

To extend the current Section 100 (Highly Specialised Drugs Program) Authority Required listing to include the treatment of:
1)WHO functional class III pulmonary arterial hypertension (PAH) secondary to scleroderma spectrum of diseases in patients who have failed to respond to prior PBS-subsidised treatment with an alternate PAH agent;
2)WHO functional class IV PAH secondary to scleroderma spectrum of diseases.

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

Epoprostenol had not previously been considered by the PBAC for PAH secondary to the scleroderma spectrum of diseases.

3. Registration Status

Epoprostenol was registered by the TGA on 15 February 2002 for the indication:

- Long term intravenous treatment of primary pulmonary hypertension (PPH) in New York Heart Association (NYHA) functional class III and class IV patients.

On 24 May 2007 the TGA registered indications for epoprostenol were extended to include:

- Long term treatment, via continuous intravenous infusion, in New York Heart Association functional class III or class IV patients with pulmonary arterial hypertension associated with the scleroderma spectrum of diseases (SSD)

The TGA registered indication was also updated in line with the reclassification of pulmonary hypertension to idiopathic and familial types as follows:

- idiopathic pulmonary arterial hypertension
- familial pulmonary arterial hypertension

4. Listing Requested and PBAC's View

The sponsor proposed that the existing epoprostenol restriction wording be extended. (Abbreviated version, **bold** text reflects requested changes).

Section 100
Highly Specialised Drugs
Public and Private Hospital Authority required
Initial (new adult patients)
Application for initial PBS-subsidised treatment with epoprostenol sodium of adult patients who have not received prior PBS-subsidised treatment with a PAH agent and who have been assessed by a physician from a designated hospital to have:
WHO Functional Class IV primary pulmonary hypertension or **pulmonary arterial hypertension secondary to scleroderma spectrum of diseases.**

Initial (new patients under 18 years of age)
Application for initial PBS-subsidised treatment with epoprostenol sodium of patients aged less than 18 years who have not received prior PBS-subsidised treatment with a PAH agent and who have been assessed by a physician from a designated hospital to have:
WHO Functional Class IV primary pulmonary hypertension or **pulmonary arterial hypertension secondary to scleroderma spectrum of diseases.**

Initial (change or re-commencement for all adult patients)
Application for initial PBS-subsidised treatment with epoprostenol sodium of adult patients with one of the following:
(a) primary pulmonary hypertension **or pulmonary arterial hypertension secondary to scleroderma spectrum of diseases** 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) WHO Functional Class IV primary pulmonary hypertension **or pulmonary arterial hypertension secondary to scleroderma spectrum of diseases** and who have received prior treatment with a PBS-subsidised PAH agent other than epoprostenol sodium; OR
(c) WHO Functional Class III primary pulmonary hypertension **or pulmonary arterial hypertension secondary to scleroderma spectrum of diseases** and who have failed to respond to a prior PBS-subsidised PAH agent.
Initial (change or re-commencement for all patients under 18 years of age)
Application for initial PBS-subsidised treatment with epoprostenol sodium of patients aged less than 18 years with one of the following:
(a) primary pulmonary hypertension **or pulmonary arterial hypertension secondary to scleroderma spectrum of diseases** 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) WHO Functional Class IV primary pulmonary hypertension **or pulmonary arterial hypertension secondary to scleroderma spectrum of diseases** and who have received prior treatment with a PBS-subsidised PAH agent other than epoprostenol sodium; OR
(c) WHO Functional Class III primary pulmonary hypertension **or pulmonary arterial hypertension secondary to scleroderma spectrum of diseases** and who have failed to respond to a prior PBS-subsidised PAH agent.

Continuing treatment (all patients)
Continuing PBS-subsidised treatment with epoprostenol sodium of patients who have received approval for initial PBS-subsidised treatment with epoprostenol sodium, 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].

Applications for authorisation must be in writing and must include:
(1) a completed authority prescription form; and
(2) a completed Pulmonary Arterial Hypertension PBS Authority Application - Supporting Information form [www.medicareaustralia.gov.au] which includes results from the 3 tests below, where available:
(i) RHC composite assessment; and
(ii) ECHO composite assessment; and
(iii) 6MWT.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Pulmonary arterial hypertension (PAH) is defined as a group of diseases characterised by a progressive increase in pulmonary vascular resistance (PVR), leading to right ventricular failure and premature death. Pulmonary arterial hypertension secondary to the scleroderma spectrum of diseases (PAH-SSD) is encompassed under the connective tissue disease (CTD) classification. These conditions share equivalent obstructive pathological changes of the

pulmonary microcirculation suggesting shared pathobiological processes among the disease spectrum of PAH .

Scleroderma is a multisystem autoimmune CTD of unknown aetiology, with an estimated prevalence of 233 cases per million. Pulmonary complications are relatively common with reports of up to 12.7% of patients developing PAH, an estimated prevalence of 29.6 cases per million. It has been estimated the five-year cumulative survival of PAH-SSD is 10% compared with 80% in a control population of patients with SSD without PAH.

The submission proposed that the place in therapy of epoprostenol in the treatment of PAH-SSD is an alternative for patients with WHO Functional Class III disease, following treatment failure with oral agents including bosentan, ambrisentan or sildenafil, and as a first line treatment option for patients with WHO Functional Class IV disease.

For PBAC's view, see Recommendation and Reasons.

6. Comparator

The submission nominated (inhaled) iloprost and (oral) bosentan as the comparators, which was considered appropriate by the PBAC.

7. Clinical Trials

The submission presented 4 studies that were used to conduct 3 indirect comparisons. Patients on conventional therapy (CT) were eligible to enrol in all the included studies. Conventional therapy included anticoagulants, diuretics, digitalis, calcium-channel blockers and supplemental oxygen.

Epoprostenol:
Study VA1A4001 was an open-label, randomised, 12-week trial which compared epoprostenol plus CT with CT in WHO FC II-IV patients with PAH-SSD.

Iloprost:
Study ME97218 was a double-blind, controlled, 12-week trial comparing iloprost with placebo in a mix of WHO FC III-IV patients with primary and secondary pulmonary hypertension (which included some PAH-SSD patients).

Bosentan:
Denton (2006) combined subgroup (PAH-CTD) data from two randomised, double-blind, placebo controlled trials (AC-052-351, a 12-week trial and AC-052-352 (BREATH-1), a 16-week trial) which compared bosentan with placebo in a mixed population of WHO FC III-IV patients with idiopathic PAH and PAH-CTD. PAH-CTD included systemic scleroderma disease and systemic lupus erythematosus.

Patients in the control arm of the open-label epoprostenol study (VA1A4001) were not administered 'placebo' (ie they were treated with CT alone) whilst the control arms of the iloprost (ME972180) and bosentan (Denton 2006) studies included placebo (CT +placebo).

The submission presented three indirect comparison analyses:

Analysis A:

This was an indirect comparison between epoprostenol, from the open-label Study VA1A4001 (that enrolled patients consistent with the requested PBS listing of epoprostenol, ie PAH-SSD), and iloprost from the double-blind study ME97218. The ITT population in Study ME97218 included a mix of patients with primary (PPH) and secondary (SPH) pulmonary arterial hypertension.

Analysis B:
This was an indirect comparison between epoprostenol from the open-label Study VA1A4001 (all PAH-SSD) and iloprost using a subgroup (SPH) of the ME97218 study population. Although this population excluded patients with primary pulmonary hypertension, it was not exclusively characterised by scleroderma disease (PAH-SSD).

Analysis C:
This was an indirect comparison between epoprostenol from the open-label Study VA1A4001 (all PAH-SSD) and bosentan from the subgroup analysis of two bosentan trials in patients with PAH-CTD (Denton (2006)). The proportion of patients with PAH-SSD from the overall PAH-CTD population was 84% (37/44) in the bosentan + CT arm and 68% (15/22) in the CT + placebo arm.

The following trials had been published at the time of submission:

Trial ID/First author	Protocol title/Publication title	Publication citation
"Common reference": CT (which included vasodilators (predominantly calcium channel blockers), digoxin, diuretics and oxygen)		
Epoprostenol		
VA1A4001		
Badesch et al.	Continuous Intravenous Epoprostenol for Pulmonary Hypertension Due to the Scleroderma Spectrum of Disease: A Randomised Controlled Trial.	Annals of Internal Medicine (2000). 132(6): 425-434.
"Common reference": Placebo plus CT		
Iloprost		
ME97218		
Olschewski et al	Inhaled iloprost for severe pulmonary hypertension.	New England Journal of Medicine . (2002). 347 (5): 322-329
Bosentan		
Denton (2006) et al.	Bosentan treatment for PAH-CTD: a subgroup analysis of the pivotal clinical trials and their open-label extensions.	Ann Rheum Dis (2006). 65: 1336-1340.
Channick et al.	Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo controlled study.	The Lancet (2001).358:1119-1123.
Badesch et al	Complete results of the first randomised placebo-controlled study of bosentan, a dual endothelin receptor antagonist, in PAH.	Current Therapeutic Research (2002) 63:227-246.
Rubin et al	Bosentan therapy for PAH.	NEJM (2002) 346 (12):896-903

PAH-SSD=Pulmonary arterial hypertension associated with secondary spectrum of diseases; PAH-CTD=Pulmonary arterial hypertension associated with connective tissue disease

8. Results of Trials

The submission used two minimum clinically important difference (MCID) thresholds (35 and 50 metres) for the indirect comparison. To establish non-inferiority, the lower bound of the 95% CI for any mean difference must be greater than -50 or -35 metres.

Epoprostenol vs iloprost

The results for the six minute walk distance (6-MWD) Endpoint are summarised in the table below:

Change from baseline at Week-12, in 6-MWD (metres) for epoprostenol and iloprost

	VA1A4001 PAH-SSD		ME97218			
			All PPH + SPH		Subgroup SPH	
	Epo + CT N=56	CT N=55	CT + *placebo* N=102	Ilo + CT N=101	CT + *placebo* N=39	Ilo + CT N=46
Mean change from baseline, m, (SD)	63.5*	**-36***	**-3.3 (74.2)**	22.2 (71.4)	**1.5 (50.3)**	-1.8 (60.7)
Difference in mean 6-MWD change: (95% CI)	Epo + CT vs CT 108* (55.2 - 180)		Ilo + CT vs CT + *placebo* 25.5 (4.2, 46.8)		Ilo + CT vs CT + *placebo* -3.3 (-26.9, 20.3)	

* Median value reported
Bolded values in "mean change from baseline" row represent the 'common' reference arms.
MCID=Minimum clinically important difference; PAH=Pulmonary arterial hypertension; PPH=Primary pulmonary hypertension; SPH=Secondary pulmonary hypertension; PAH-SSD=Pulmonary arterial hypertension secondary to scleroderma disease; CT=Conventional therapy; Ilo=Iloprost; Epo=Epoprostenol; CI=Confidence interval; 6-MWD=6 Minute walk distance; SD=Standard deviation.

The submission concluded that despite the limitations of the indirect comparison, these results suggested that epoprostenol is at least as effective as iloprost in terms of this primary outcome and possibly superior by a clinically important margin.

Haemodynamic Endpoints:

There were no haemodynamic data specifically for the SPH subgroup from the iloprost study, ME97218. Thus data from this study included a mix of PPH and SPH, as presented below:

Haemodynamic parameters (rounded to one decimal place)

Study	Treatment (N)	Mean change from baseline	Standard Error	Mean difference, active vs control (95% CI)
PVRm (mmHg/litre/min)				
VA1A4001	Epo + CT, N=47	-4.6	-0.8	-5.5 (-7.3, -3.7)
	CT, N=44	0.9	0.6	
ME97218	CT + *placebo*, N=77	1.2	0.1	-4.2 (-5.0, -3.5)
	Ilo + CT, N=70	-3.0	-0.4	
PAPm (mmHg)				
VA1A4001	Epo + CT, N=50	-5.0	1.1	-5.9 (-7.3 -4.5)
	CT, N=48	0.9	1.1	
ME97218	CT + *placebo*, N=82	-0.2	-0.0	-4.4 (-5.4, -3.5)
	Ilo + CT, N=90	-4.6	-0.5	

EPO=Epoprostenol; ILO=Iloprost; BOS=Bosentan; CT=Conventional therapy; PAPm=Mean pulmonary arterial pressure; PVRm=Mean pulmonary vascular resistance; PPH=Primary pulmonary hypertension; SPH=Secondary pulmonary hypertension.

The submission concluded that the results of the indirect comparison between epoprostenol and iloprost, in terms of haemodynamic parameters, favoured epoprostenol although any observed differences were not statistically significant.

Epoprostenol vs bosentan:
The results for the 6-MWD End point are summarised in the table below:

6-MWD results for epoprostenol and bosentan (rounded to one decimal place)

	VA1A4001 PAH-SSD		Denton (2006) All PAH-CTD	
	Epo + CT N=56	CT N=55	CT + *placebo* N=22 *15/22 (68%): PAH-SSD*	Bosentan + CT N=44 *37/44 (84%): PAH-SSD*
Mean change from baseline, m, (SD)	63.5*	**-36***	**-2.6 (122.9)**	19.5 (76.8)
Difference in mean 6-MWD change: (95% CI)	Epo + CT vs CT 108* (55.2 – 180.0)		Bosentan + CT vs CT + *placebo* 22.1 (-32.0, 76.0)	

* Median values reported.
Bolded values in "mean change from baseline" row represent the 'common reference' arms.
MCID=Minimum clinically important difference; PAH-CTD=Pulmonary arterial hypertension secondary to connective tissue disease; PAH-SSD=Pulmonary arterial hypertension secondary to scleroderma disease; CT=Conventional therapy; Epo=Epoprostenol; CI=Confidence interval; 6-MWD=6 Minute walk distance; SD=Standard deviation.

The submission concluded that the indirect comparison favoured epoprostenol treatment at Week 12 when compared to bosentan treatment, although this result was not statistically significant.

For PBAC's view of these results, see Recommendation and Reasons.

The following summarises the key adverse events (AEs) across the studies included for the indirect comparison:

- There was a higher proportion of AEs in the epoprostenol + CT arm vs CT arm in terms of, depression, diarrhoea, jaw pain, nausea and anorexia.
- In Study ME97218, the proportion of patients who experienced an AE was similar (approximately 90%) between the iloprost + CT arm and the CT + placebo arm. However, more patients in the iloprost + CT arm vs the CT + placebo arm had vomiting, vasodilation, jaw pain, hypotension, headache and increased cough; and
- In Denton (2006), a higher proportion of patients in the bosentan + CT arm vs CT + placebo arm experienced dizziness, fatigue and lower limb oedema.

Safety extension study VA1A4002: This study was an extension study to Study VA1A4001 designed to provide long term safety data. The key conclusions made by the FDA review of these data were:

- Patients who died tended to have a longer history of pulmonary hypertension and scleroderma disease;
- 34% of patients experienced serious adverse events. These events included right heart failure, sepsis, hypotension and pneumonia;
- 22% of patients experienced adverse events attributable to the drug delivery system. These events included injection site pain, reaction and haemorrhage, sepsis and cellulitis;
- 22/99 (24%) patients had died when the FDA review was conducted. The FDA review notes that although the majority of deaths were due to right heart failure, in several cases, sepsis (likely associated with the central line) and /or hypotension (likely due to epoprostenol) were the primary causes of the observed mortality.

The most recent Periodic Safety Update Report (PSUR) did not indicate any new safety issues beyond those established for epoprostenol.

9. Clinical Claim

The submission described epoprostenol as non-inferior in terms of effectiveness and non-inferior in terms of safety compared to the main comparators, iloprost and bosentan.

The PBAC considered that the submission's claim that epoprostenol is non-inferior to bosentan and iloprost in terms of comparative efficacy is reasonable based on the submitted data. The PBAC noted that while the comparative safety of these PAH drugs is difficult to assess in the absence of head-to head trial data, the safety profiles are well recognised and the safety of epoprostenol is comparable across all subgroups of PAH patients.

10. Economic Analysis

The submission presented a cost minimisation analysis.

The cost analysis included pharmaceutical costs, costs associated with administration of the drug, and costs associated with management of treatment-related adverse events.

The estimated equi-effective doses are epoprostenol, commencing at a dose of 2.2 ng/kg/min, with an average dose of 11.2 ng/kg/min at week 12, increasing linearly in steps to an average dose of 47.4 ng/kg/min at 3 years; bosentan 62.5 mg orally twice daily for 4 weeks, then a maintenance dose of 125 mg twice daily; and iloprost 2.5-5 µg nebulised 6-9 times per day, giving a mean of 7.5 x 20 µg (7.5 x 1 ampoule) per day.

11. Estimated PBS Usage and Financial Implications

The likely number of patients treated was estimated by the submission to be less than 10,000 over the first 5 years. The estimate was considered uncertain.

The submission estimated there would be net financial savings to the PBS.

12. Recommendation and Reasons

The PBAC recommended listing epoprostenol on the PBS in the Section 100 (Highly Specialised Drugs Program) as a Public and Private Hospital Authority Required benefit for second-line therapy for WHO functional class III pulmonary arterial hypertension (PAH) secondary to connective tissue disease and first line therapy for WHO functional class IV PAH secondary to connective tissue disease on a cost minimisation basis compared with iloprost and bosentan. The equi-effective doses are estimated to be epoprostenol, commencing at a dose of 2.2 ng/kg/min, with an average dose of 11.2 ng/kg/min at week 12, increasing linearly in steps to an average dose of 47.4 ng/kg/min at 3 years; bosentan 62.5 mg orally twice daily for 4 weeks, then a maintenance dose of 125 mg twice daily; and iloprost 2.5-5 µg nebulised 6-9 times per day, giving a mean of 7.5 x 20 µg (7.5 x 1 ampoule) per day.

The PBAC noted that the requested listing specifies scleroderma spectrum of diseases (SSD) whereas the restriction for the comparators bosentan and iloprost specifies scleroderma and connective tissue disease (CTD) respectively, consistent with the relevant TGA registrations. The PBAC noted the potential for subjective interpretation of the PAH SSD and CTD listings

as CTDs are a spectrum of disorders of which scleroderma is a subset. The PBAC considered that the restriction wording be changed to connective tissue disease and that there should be consistency across the PAH group of drugs. This should be done in consultation with the Thoracic Society of Australia and New Zealand (TSANZ). The PBAC recommended no age-restriction in the listing for consistency with other PBS-listed PAH drugs.

The PBAC considered that the nominated comparators, bosentan and iloprost are appropriate.

The PBAC noted that head-to-head studies of PAH drugs are limited but recalled that it has previously accepted the claim for non-inferiority for PAH drugs based on non-statistically significant results for the six minute walk distance (6-MWD). The PBAC noted the outcomes of the indirect comparison of Study VA1A4001 and ME97218 of epoprostenol versus iloprost and Study VA1A4001 and Denton 2006 of epoprostenol versus bosentan based on the common comparator conventional therapy (CT). The difference was evaluated by a change in baseline at Week 12 in the 6-MWD. To establish non-inferiority the lower bound of the 95% CI for any mean difference must be greater than -50 or -35 metres. The PBAC concluded from the indirect comparison that any haemodynamic parameters favouring epoprostenol over iloprost were not statistically significant but the indirect analysis suggested that based on the differences in 6-MWD that epoprostenol was non-inferior, consistent with the minimal clinically important difference (MCID). The PBAC also concluded that epoprostenol is non-inferior to bosentan based on the indirect analysis meeting the specified criteria for non-inferiority.

Therefore, the PBAC considered that the submission's claim that epoprostenol is non-inferior to bosentan and iloprost in terms of comparative efficacy is reasonable based on the submitted data. The PBAC noted that while the comparative safety of these PAH drugs is difficult to assess in the absence of head-to head trial data, the safety profiles are well recognised and the safety of epoprostenol is comparable across all subgroups of PAH patients.

Recommendation:
Epoprostenol sodium, powder for I.V. infusion, 500 micrograms (base) with diluent, 1.5 mg (base) with diluent

(Epoprostenol sodium, powder for I.V.infusion, 500 micrograms and 1.5 mg (base) with diluent, cassette reservoir and extension set

Extend the current restriction to include:

Restriction:	**To be finalised** Section 100 Highly Specialised Drugs Program Public and Private Hospital Authority Required
Maximum qty:	1 (500 microgram, 1.5 mg)
Rpt:	Nil

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 is satisfied with the PBAC decision. This decision will allow for consideration of the future listing of epoprostenol, as an important alternative medicine, for the treatment of pulmonary arterial hypertension secondary to connective tissue disease.