

# **Pulmonary Arterial Hypertension (PAH) medicines utilisation analysis**

## **Drug utilisation sub-committee (DUSC)**

*February 2015*

### **Abstract**

#### **Purpose**

To assess the utilisation of medicines listed on the Pharmaceutical Benefits Scheme (PBS) for the treatment of pulmonary arterial hypertension (PAH).

Following the listing of sitaxentan in April 2008, the DUSC requested that the Secretariat maintain a watching brief on the utilisation of the group of medicines used in the treatment of PAH. Consequently an analysis of PAH medicines was presented to DUSC at its June 2010 meeting. The current report updates and enhances this report.

#### **Date of listing on PBS**

- bosentan: 1 March 2004
- iloprost: 1 April 2005
- epoprostenol: 1 August 2006
- sildenafil: 1 March 2007
- sitaxentan: 1 April 2008, delisted 31 March 2011
- ambrisentan: 1 December 2009
- tadalafil: 1 April 2012
- macitentan: 1 September 2014

#### **Data Source / methodology**

- PBS pharmacy claims data from the DUSC database and the Department of Human Services (DHS) prescription databases.
- Authority Approval data from the DHS Authority Approval database

#### **Key Findings**

- The number of patients starting on a PAH medicine for the first time is steady at approximately 420 patients each year. Until mid-2014, bosentan was the most

frequently prescribed first PAH medicine. Macitentan has become the most common medicine for new patients since it was listed on 1 September 2014.

- The number of prevalent patients continues to increase over time, presumably due to improved survival. There were 2026 prevalent patients in 2013.
- The age of patients initiating treatment has increased over the last decade. The mean age of new patients was 53.2 years in 2003/04 and 64.1 years in 2013/14. This compares with a mean age of 48.8 years in patients in the bosentan arms of the key clinical trials.
- The mean time on treatment was 4.63 years (all excluding breaks) and 4.72 years (all including breaks).
- The average prescribed dose of epoprostenol is higher than expected. This may reflect treatment of a more severe population as epoprostenol is restricted to class IV patients. However the cost-effectiveness of higher doses is not known.

## Purpose of analysis

To assess the utilisation of medicines listed on the Pharmaceutical Benefits Scheme (PBS) for the treatment of pulmonary arterial hypertension.

Following the listing of sitaxentan in April 2008, the DUSC requested that the Secretariat maintain a watching brief on the utilisation of the group of medicines used in the treatment of PAH. Consequently an analysis of PAH medicines was presented to DUSC at its June 2010 meeting. The current report updates and enhances this report.

## Background

### Pharmacology

The PBS listed medicines for PAH fall into three classes:

Endothelin receptor antagonists	bosentan, sitaxentan, ambrisentan, macitentan
Synthetic prostacyclin /prostacyclin analogues	epoprostenol, iloprost
Phosphodiesterase type-5 (PDE5) inhibitors	sildenafil, tadalafil

Further information on the pharmacological action can be obtained from the Product Information which is available from the [TGA \(Product Information\)](#).

### Therapeutic Goods Administration (TGA) approved indications

The functional classes for which each agent is TGA approved are noted below:

- sildenafil and tadalafil are indicated for class II and III symptoms only
- bosentan, ambrisentan and macitentan are indicated for class II, III and IV
- iloprost is indicated for class III and IV only
- iloprost is indicated for moderate to severe disease.

The TGA approved indications are summarised in Appendix A.

### Dosage and administration

The dosing and administration information in Table 1 is sourced from the Product Information, which is available from the [TGA website \(Product Information\)](#).

Table 1: recommended dosage of PAH drugs

PAH drug	Route	Recommended dosage for adults
Bosentan	oral	Initially 62.5 mg twice daily for 4 weeks. Increase to a maintenance dose of 125 mg twice daily. Doses above 125 mg twice daily did not appear to confer additional benefit sufficient to offset the increased risk of liver injury.
Sitaxentan	oral	100 mg daily

PAH drug	Route	Recommended dosage for adults
Ambrisentan	oral	5 mg once daily. Additional benefit may be obtained by increasing the dose to 10 mg.
Macitentan	oral	10 mg once daily. Doses higher than 10 mg daily have not been studied and are not recommended.
Sildenafil	oral	20 mg three times a day (TID) No greater efficacy was achieved with doses higher than 20 mg TID, and therefore are not recommended. Dosages lower than 20 mg TID have not been examined and the efficacy is not known.
Tadalafil	oral	40 mg (2 x 20 mg) taken once daily
Iloprost	inhaled (nebulised)	At initiation the first inhaled dose should be 2.5 microgram (mcg) iloprost. If this dose is well tolerated, dosing should be increased to 5.0 mcg and maintained at that dose. In case of poor tolerability of the 5.0 mcg dose, the dose should be reduced to 2.5 mcg. Inhalations are administered 6 to 9 times per day during waking hours according to the individual need and tolerability. The duration of an inhalation session is approximately 4 to 10 minutes.
Epoprostenol	continuous intravenous infusion	The following schedules have been found effective: <i>Short-term (acute) dose-ranging:</i> A short-term dose-ranging procedure administered via either a peripheral or central venous line is required to determine the long-term infusion rate. The infusion rate is initiated at 2ng/kg/min and increased by increments of 2 ng/kg/min every 15 minutes or longer until maximum haemodynamic benefit or dose-limiting pharmacological effects are elicited. <i>Long-term continuous infusion</i> is administered through a central venous catheter. Long-term infusions should be initiated at 4 ng/kg/min less than the maximum tolerated infusion rate determined during short-term dose-ranging. If the maximum tolerated infusion rate is 5 ng/kg/min or less, then the long-term infusion should be started at 1 ng/kg/min.

For all of these medicines treatment should only be initiated and monitored by a physician experienced in the treatment of pulmonary arterial hypertension.

Serum liver aminotransferase (AST & ALT) levels must be measured prior to initiation of treatment with bosentan, ambrisentan and macitentan. Monthly monitoring during treatment is recommended.

Full information on dosage and administration, monitoring requirements and drug interactions are available from the Product Information.

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from [the TGA \(Product Information\)](#) and [the TGA \(Consumer Medicines Information\)](#).

## **Clinical situation**

PAH is one of five clinical classifications of pulmonary hypertension (PH)<sup>1</sup>. The clinical classifications have evolved over time as the understanding of PH has progressed.

Group 1: Pulmonary Arterial Hypertension (previously called primary pulmonary hypertension)

Group 2: PH due to left heart disease

Group 3: PH due to chronic lung diseases and/or hypoxia

Group 4: Chronic thromboembolic pulmonary hypertension (CTEPH)

Group 5: PH with unclear multifactorial mechanisms

Within PAH there are further subcategories including idiopathic, hereditary, drug and toxin induced, and PAH associated with connective tissue disease, HIV infection, portal hypertension, congenital heart disease or schistosomiasis<sup>1</sup>.

The World Health Organization (WHO) defines four functional classifications of PAH depending on symptom severity:

Class I: No limitation of usual physical activity. Ordinary physical activity does not cause increased dyspnoea, fatigue, chest pain, or presyncope.

Class II: Mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnoea, fatigue, chest pain, or presyncope.

Class III: Marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnoea, fatigue, chest pain, or presyncope.

Class IV: Unable to perform any physical activity without symptoms and may have signs of right ventricular heart failure. Dyspnoea and/or fatigue may be present at rest.

Physical activity tolerance in PAH is often assessed by the 6-minute-walk distance test. This test has been the basis for inclusion criteria and primary end points of many clinical trials of PAH medicines. Together with right heart catheter and echocardiograph composite assessments, the PBS restrictions use the 6-minute walk test to establish a patient's baseline measurements and response to treatment.

## **Definition**

PH has been defined as an increase in mean pulmonary arterial pressure (PAP) to  $\geq 25$  mmHg at rest as assessed by right heart catheterisation (RHC).<sup>2</sup>

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<sup>1</sup> Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2013; 62(25 Suppl):eD34-e41. doi: 10.1016/j.jacc.2013.10.029.

Eligibility for PBS medicine subsidy requires evidence of PAH defined as a mean pulmonary artery pressure (mPAP) greater than 25 mmHg at rest and pulmonary artery wedge pressure (PAWP) less than 15 mmHg. Where a right heart catheter (RHC) cannot be performed on clinical grounds, PAH is defined as right ventricular systolic pressure (RVSP), assessed by echocardiography (ECHO), greater than 40 mmHg, with normal left ventricular function.

A previous definition of PH on exercise as a mean PAP >30mmHg as assessed by RHC has been found to not be supported by published data and has been removed from current accepted definitions<sup>3</sup> and from the PBS restrictions.

## **PBS listing and restriction details (as at December 2014)**

Prescribing of PBS subsidised PAH medicines requires prior written Authority approval from the Department of Human Services.

The restrictions are complex. Not all medicines are available for both class III and class IV PAH, and definitions and terminology have been updated over time.

The full PBS restrictions current at the time of this report (December 2014) and versions of restrictions from previous schedules are available at [pbs.gov.au](http://pbs.gov.au).

Common elements of the current restrictions for the 7 listed PAH agents (bosentan, ambrisentan, macitentan, iloprost, epoprostenol, sildenafil, tadalafil) are as follows:

- Patients are eligible for PBS subsidised treatment with 1 PAH agent at any time.
- Patients must have been assessed by a physician from a designated hospital
- Patients with WHO functional Class III with mean right arterial pressure (mRAP)  $\leq$  8 mm Hg must have failed to respond to 6 or more weeks of appropriate vasodilator treatment unless contraindicated or intolerant
- PAH is defined as a mean pulmonary artery pressure (mPAP) greater than 25 mmHg at rest and pulmonary artery wedge pressure (PAWP) less than 15 mmHg. Where a right heart catheter (RHC) cannot be performed on clinical grounds, PAH is defined as right ventricular systolic pressure (RVSP), assessed by echocardiography (ECHO), greater than 40 mmHg, with normal left ventricular function.
- Results of a RHC composite assessment, plus an ECHO composite assessment, plus a 6 minute walk test (6MWT) must be provided unless contraindicated on medical grounds. See full restriction for details.

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<sup>2</sup> McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *J Am Coll Cardiol* 2009;53:e1573–e619. doi:10.1016/j.jacc.2009.01.004.

<sup>3</sup> Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009; 30(20): e2493–e537. doi: 10.1093/eurheartj/ehp297.

- A minimum of 2 test results must qualify for each continuation or change application where the patient has demonstrated stability or improvement relative to baseline.
- Patients are eligible to change or re-commence after a break in therapy but are not eligible to receive further PBS subsidised treatment with an agent to which they have previously failed to demonstrate stability or improvement.
- Patients with PAH secondary to interstitial lung disease associated with connective tissue disease, where the total lung capacity is less than 70 per cent of that predicted, are not eligible for PBS subsidised treatment.

The clinical and functional classifications of PAH that are currently PBS subsidised for patients initiating PAH therapy are summarised in Table 1. In summary:

- sildenafil and tadalafil are restricted to the treatment of WHO functional class III patients.
- epoprostenol is restricted to the treatment of WHO functional class IV patients (Note: epoprostenol is also subsidised for WHO FC III patients as a 2nd line option in patients who have failed to respond to a prior PBS subsidised agent, but not as a 1<sup>st</sup> line option).
- bosentan and macitentan are the only PBS listed medicines for PAH associated with a congenital systemic-to-pulmonary shunt (including Eisenmenger’s physiology).
- iloprost is the only drug with the broader drug-induced PAH listing i.e. not just anorexigen induced.

**Table 1: Summary of PBS restriction by drug**

	Bosentan	Ambrisentan	Macitentan	Sildenafil	Tadalafil	Iloprost	Epoprostenol
Class III iPAH	✓	✓	✓	✓	✓		
Class III anorexigen-induced	✓	✓	✓	✓	✓		
Class III drug-induced						✓	
Class III hereditary	✓	✓	✓	✓	✓		
Class III secondary to connective tissue disease	✓	✓	✓	✓	✓		
Class IV anorexigen-induced	✓	✓	✓			✓	✓
Class IV drug-induced						✓	
Class IV hereditary	✓	✓	✓			✓	✓
Class IV secondary to connective tissue disease	✓	✓	✓			✓	✓
Class III or IV congenital systemic-to-pulmonary shunt	✓		✓				

Figure 1 shows a schematic summary of the PBS restriction for patients initiating PAH therapy.

The original restrictions of the above drugs (excluding macitentan) referred to “primary pulmonary hypertension”, “pulmonary arterial hypertension secondary to connective tissue disease” and “pulmonary arterial hypertension associated with a congenital systemic-to-

pulmonary shunt (including Eisenmenger's physiology)". The terminology and restrictions were updated from 1 August 2014 following a request from the Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ):

- The existing single term "Primary Pulmonary Hypertension" was replaced by the terms "Idiopathic Pulmonary Arterial Hypertension (iPAH), anorexigen- induced PAH and hereditary PAH".
- The term "pulmonary capillary wedge pressure (PCWP)" was replaced by "Pulmonary Artery Wedge Pressure" and the cut-point for this parameter was lowered from <18mmHg to <15mmHg to comply with International Guidelines.
- The reference to a mPAP >30mmHg on exercise was removed as part of the definition of Pulmonary Hypertension

In line with the current restriction, this report does not use the term "primary pulmonary hypertension", except in the "Relevant aspects of PBAC considerations" section which refers to the PBAC recommendations using the terminology current at the time and in the TGA approved indication section in cases where this terminology remains in the Product Information.

The DHS initial and continuing written authority application supporting information forms, which are based on the PBS restriction, are useful for understanding the PBS restriction. These can be downloaded from the DHS website ([Initial authority](#), [Continuing authority](#)).

The complete PBS listings (restrictions and item codes) for the medicines used to treat PAH can be accessed from [the PBS website](#).

Figure 1 provides a summary of the PBS restriction for patients initiating PAH therapy.

### ***Date of listing on PBS***

Appendix C summarises the listing history for the PAH PBS items.

# Schematic diagram of PBS restriction for patients initiating PAH therapy

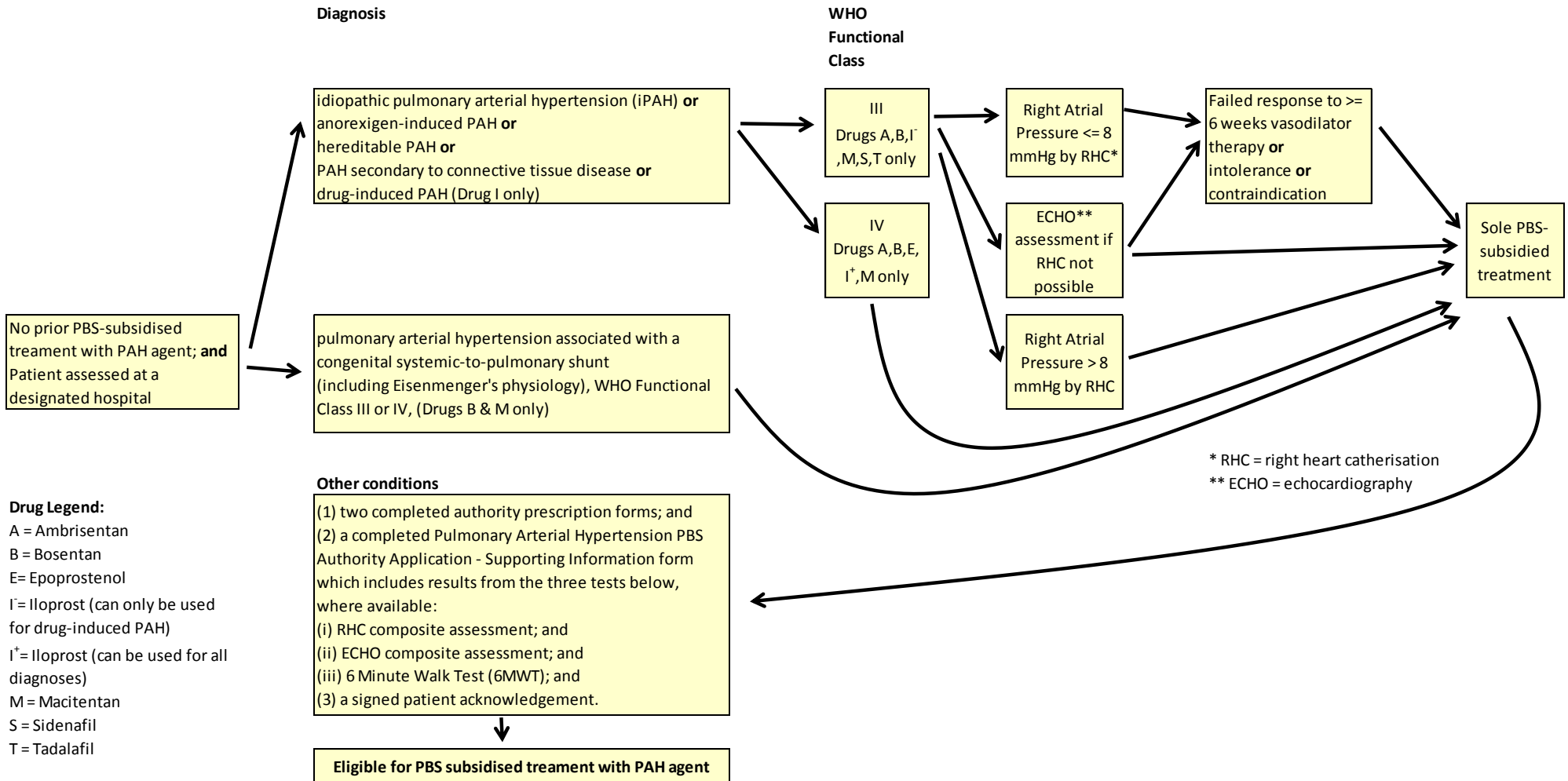


Figure 1: PBS restriction summary for patients initiating PAH therapy

## Relevant aspects of the PBAC consideration

Table 2 provides a chronological summary of PBAC recommendations for PAH medicines. Briefly, bosentan was the first medicine listed and this was on a cost-effectiveness basis compared with standard care, which included the use of supplemental oxygen, digitalis, diuretics, vasodilators, anticoagulants, or lung transplantation and repair. All medicines since have been recommended on a cost-minimisation basis to bosentan, except tadalafil, which was cost-minimised to sildenafil and riociguat (recommended but not yet listed as at 1 November 2014) which was cost minimised to a mixed comparator of bosentan and sildenafil. For further detail refer to the [Public Summary Documents](#).

**Table 2: Summary of PBAC considerations by drug**

PBAC meeting	Medicine	Basis for recommendation
Dec 2003	Bosentan	WHO functional Class III or IV patients with primary PH or PAH secondary to scleroderma (a connective tissue disease), on the basis of an acceptable, but high, cost-effectiveness ratio. The recommendation was considered in the context of a risk-sharing agreement (which included a patient registry to examine survival funded to run for three years), the proposal to limit prescribing to clinicians from designated hospitals and the proposed inclusion of the continuation rule in the restriction. The main uncertainty at this time was the modelled survival gain beyond the trial duration.
Nov 2004	Iloprost	WHO functional Class III or IV patients with primary PH, PAH secondary to connective tissue disease or drug-induced PAH (appetite suppressants) on a cost-minimisation basis compared with bosentan, with the equi-effective doses being iloprost 2.5-5 micrograms nebulised 6-9 times per day, giving a mean of 7.5 x 20 micrograms (i.e. 7.5 x one ampoule) consumed per day, and bosentan 125 mg taken twice daily. From 1 August 2009 iloprost was restricted to class IV, and class II/IV drug-induced PAH.
Mar 2006	Epoprostenol	WHO functional Class III or IV patients with primary PH, on a cost-minimisation basis with bosentan. The equi-effective doses are poprostenol, commencing at an average dose of 11.9 ng/kg per minute (continuous infusion) over the first three months of treatment and escalating linearly in steps to an average dose of 27.2 ng/kg per minute at 3 years, and bosentan 125 mg twice a day. From 1 August 2009 poprostenol was restricted to Class IV only.
Nov 2006	Sildenafil	WHO functional Class III patients with primary PH or PAH secondary to connective tissue disease, on a cost minimisation basis compared with bosentan. The equi-effective doses are sildenafil 20 mg three times daily and bosentan 125 mg twice daily.
Jul 2007	Sitaxentan	WHO functional Class III patients with primary PH or PAH secondary to connective tissue disease on a cost-minimisation basis compared to bosentan. The equi-effective doses are sitaxentan 100 mg daily and bosentan 125 mg twice daily. Sitaxentan was delisted because on December 10, 2010 Pfizer announced it would be withdrawing the drug worldwide (both from marketing and from all clinical study use), citing that it is a cause of fatal liver damage.
Mar 2008	Bosentan	Pulmonary arterial hypertension associated with congenital systemic-to-pulmonary shunts including Eisenmenger's physiology (APAH-CHD) based on acceptable cost-effectiveness compared with standard care.
Jul 2009	Ambrisentan	WHO functional Class III or IV patients with primary PH and PAH secondary

PBAC meeting	Medicine	Basis for recommendation
		to connective tissue disease on a cost minimisation basis compared with bosentan. The equi-effective doses are ambrisentan 5mg daily and bosentan 125 mg twice daily.
Nov 2011	Tadalafil	Primary PH and PAH secondary to connective tissue disease Functional Class III on a cost minimisation basis compared with sildenafil. The equi-effective doses are tadalafil 40 mg (2 x 20 mg once daily) and sildenafil 60 mg (20 mg three times a day).
Mar 2014	Macitentan	Idiopathic PAH, PAH secondary to connective tissue disease (PAH-CTD) and PAH associated with congenital heart disease (PAH-CHD) in patients with WHO Functional Class III and IV severity on a cost minimisation basis to bosentan. The equi-effective doses were estimated as macitentan 10mg once daily versus bosentan 62.5mg twice daily for 4 weeks, then a maintenance dose of 125mg twice daily.
Mar 2014	Riociguat	Primary PH, PAH secondary to connective tissue disease and PAH associated with congenital heart disease (CHD) in patients with WHO Functional Class III / IV severity on a cost minimisation bases with a mixed comparator of bosentan and sildenafil. The equi-effective doses being individual titration of riociguat (1 mg tid to 2.5 mg tid) and bosentan 62.5 mg bid or 125 mg bid, and individual titration of riociguat (1 mg tid to 2.5 mg tid) and sildenafil 20 mg tid. Not yet listed as at 1 November 2014.
July 2014	Epoprostenol	Listing of additional brand, Veletri®. The PBAC recommended listing at the price proposed in the submission, noting that this price incorporated a 16% price reduction compared to the currently listed Flolan® brand. The listing was effective 1 August 2014.

At the November 2013 meeting, the PBAC considered correspondence from the Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ). The Society agreed for this correspondence to be provided for context in this DUSC report.

## Previous analyses by DUSC

Following the listing of sitaxentan in April 2008, DUSC requested that the Secretariat maintain a watching brief on the utilisation of the group of medicines used in the treatment of PAH. Consequently an analysis of PAH medicines was presented to DUSC at its June 2010 meeting. The following is an extract of the minutes of that meeting relating to the PAH analysis.

*The DUSC noted the increasing use of bosentan. The pattern of use was considered and members commented that PAH is likely to be a disease with constant and low prevalence. According to Medicare approvals, initiating numbers for bosentan are steady at around 20 per month. There is more variability in much lower numbers initiating other PAH drugs. The Committee also noted the continuing rise in overall treatment costs and drug use. This may be explained by people living longer with the disease. The possibility of sequential use and some co-prescribing of these drugs was acknowledged. Co-prescribing through the PBS is unlikely as these drugs have to be approved through Medicare Australia Tasmania (prior written approval of complex drugs); however sildenafil is available at reasonably low cost to the private market.*

*The doses of epoprostenol provided in the analysis were questioned. Members were concerned that the choice of vial may be influencing costs which seem inconsistent with the pricing approach when listed.*

The current report updates and enhances the 2010 DUSC analysis.

## **Methods**

The analysis includes utilisation for the total PBS-subsidised PAH market and the individual medicines.

PBS/RPBS prescription approvals for PAH medicines were extracted from the Department of Human Services (DHS) PBS Authority Approval database for the period March 2004 to September 2014 inclusive, based on the date that the prescription was approved.

The number of prevalent patients was determined by counting the number of person specific numbers (non-identifying) in the authority approval data for the specified time period. Authority approvals data was used rather than prescription supply data as the latter is incomplete with respect to patient level supply history for PAH drugs prior to July 2013 (see Appendix B for further information). The median times to re-supply by drug (also in Appendix B) show that the longest median time to resupply is 37 days for iloprost. This means that to capture all prevalent patients in the data, given that most have one original and five repeats, the period over which prevalence needs to be calculated is greater than 6 months. Thus in this report prevalence is calculated over a period of a year to avoid underestimation.

New (initiating) patients were defined as those with no prior PBS or RPBS authority approval for the drug or drug group of interest.

Pack and prescription utilisation data were extracted from the DUSC HSD database for the period March 2004 to June 2014 inclusive. The DUSC HSD database combines Public Hospital prescribed offline processed data with Public and Private Hospital prescribed online processed data to give a complete picture of HSD drug utilisation. Note that pack and prescription supply data was only available until the end of June 2014, whereas the authority approval data was available to September 2014. This is because of the significantly longer lag from pack supply to DHS processing of claims compared to the lag from approval to the approval data being available to the Department of Health.

Patient demographic information was derived from data extracted from the DHS supplied prescription database. The information was merged with the authority approval data to get initiating and prevalent patient counts by age and gender (see Figure 9).

Length of treatment analysis was performed using DHS supplied prescription data using the methodology described in Appendix B. As noted above, this data is incomplete with respect to patient level supply history for HSDs prior to July 2013. The extent of this incompleteness was investigated (see Appendix B) and was not large. The impact of this slight incompleteness was tested in the analysis by comparing results from Victorian hospitals,

which have 100% complete patient level data, with results from other states. Length of treatment analyses used prescription data from March 2004 to July 2014 inclusive.

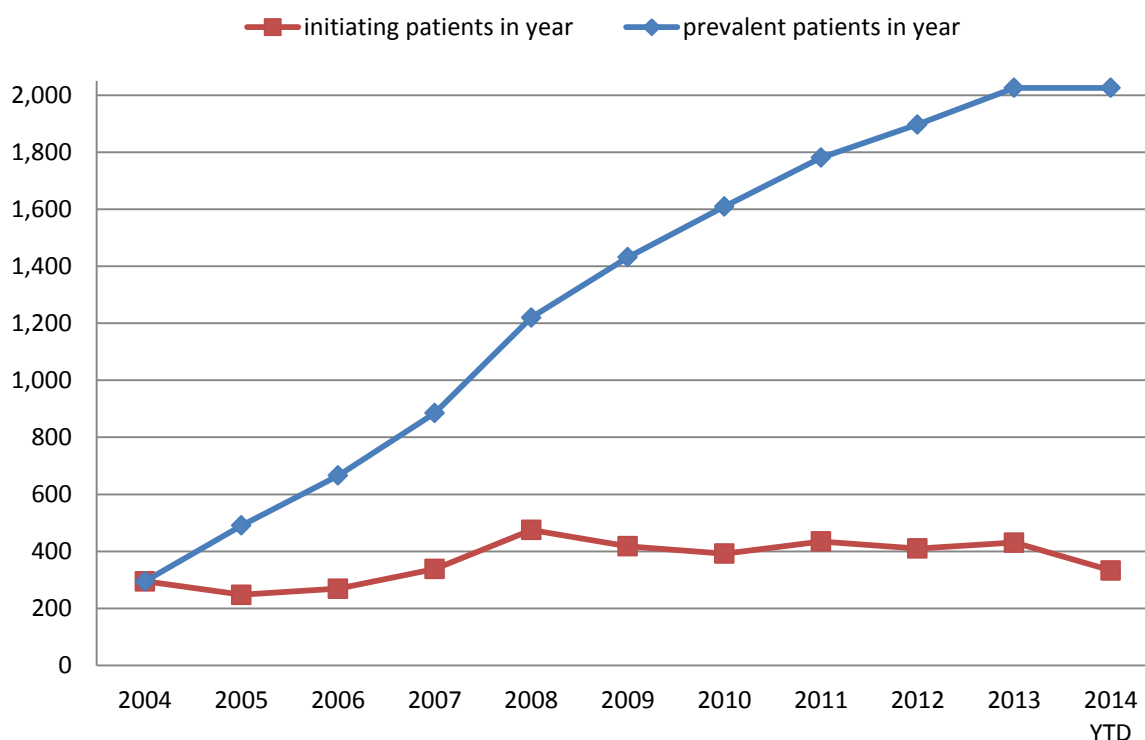
The dosage information in the 'Estimated prescribed dose' section comes from the quantity and strength information recorded in the DHS Authorities Approval database for approvals from 2013 Q3 to 2014 Q2 inclusive. The actual prescribed dose is not recorded in the database. The prescribed dose was estimated from the approval data by assuming the quantity prescribed on each prescription is intended by the prescriber to be for 30 days of treatment (except for tadalafil which has a pack size of 56 tablets so it assumed to be intended for 28 days) and summing the approvals for different strengths of a drug for a patient on a day, having regard to both the strength and the quantity requested.

Data analysis was undertaken using SAS.

## Results

### Analysis of drug utilisation

Figure 2 shows the number of patients initiating a PAH medicine for the first time, and the total number of patients treated with a PAH medicine (prevalent population), each year.



**Figure 2: Patients - initiating and prevalent to PAH treatment, based on authority approvals**

Source: DHS Authority Approvals database

Note: Prevalence in 2004 is calculated from only 10 months of data as the first PAH drug (bosentan) was listed in March 2004. Prevalence in 2014 YTD is calculated from only the first 3 quarters of data (i.e. until the end of September 2014).

The number of initiators has remained steady since 2009. The number of prevalent patients has not yet plateaued, indicating a relatively long average time on treatment (the apparent plateau in 2014 YTD is because the year is incomplete).

There are no published national prevalence and incidence figures for PAH in Australia. Peacock et al.<sup>4</sup> reported that total PAH prevalence and incidence ranged from 15 to 52 and 2.4 to 7.6 per million population respectively using three sources, one from France and two

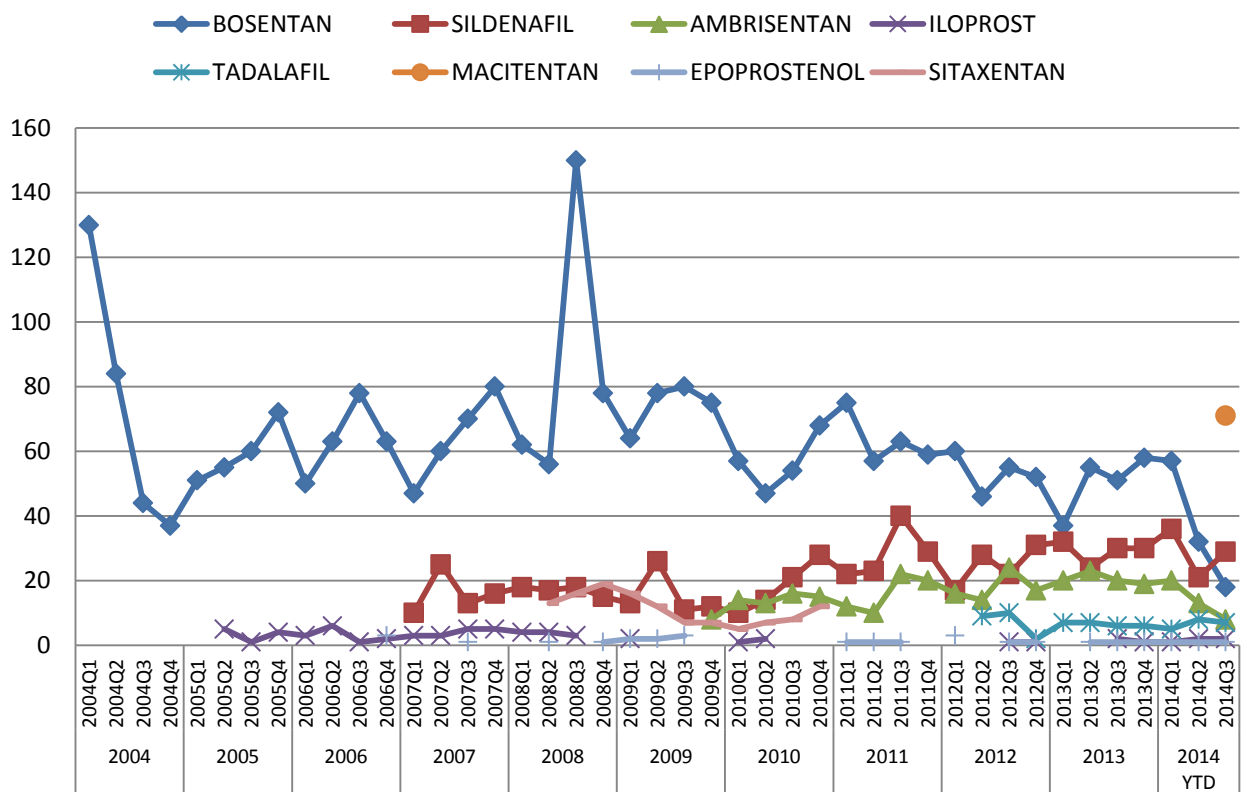
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<sup>4</sup> Peacock AJ, Murphy NF, McMurray JJ, Caballero L, Stewart S. An epidemiological study of pulmonary arterial hypertension. *Eur Respir J* 2007; 30:e104–e109. Doi: 10.1183/09031936.00092306

from Scotland. Jansa et al.<sup>5</sup> reported prevalence estimates of PAH between 15 to 26 cases per million adults from several sources, including Scotland, France, Spain, Switzerland and the USA. They also estimate prevalence and incidence for adults in the Czech Republic in 2007 as 22.4 and 10.7 cases per million persons respectively.

Using the data in Figure 2 for 2013 the number of prevalent and incident patients on PAH treatment are 2,026 and 431 respectively. If this is divided by the total Australian population as at 30 June 2013 (23.13 million) the prevalent and incident rates of PAH treatment are 87.6 and 18.6 per million population. This is considerably higher than any of the above published estimates.

Figure 3 breaks down the initiators shown in Figure 2 by the medicine they used to initiate PAH therapy. In total 4,044 patients have initiated PAH therapy over the period March 2004 to September 2014 inclusive.



**Figure 3: Patients - initiating to PAH therapy by initiating drug, based on authority approvals**

Source: DHS Authority Approvals database

Note: Macitentan was listed on the 1/9/2014 and so 2014 Q3 only contains one month of data

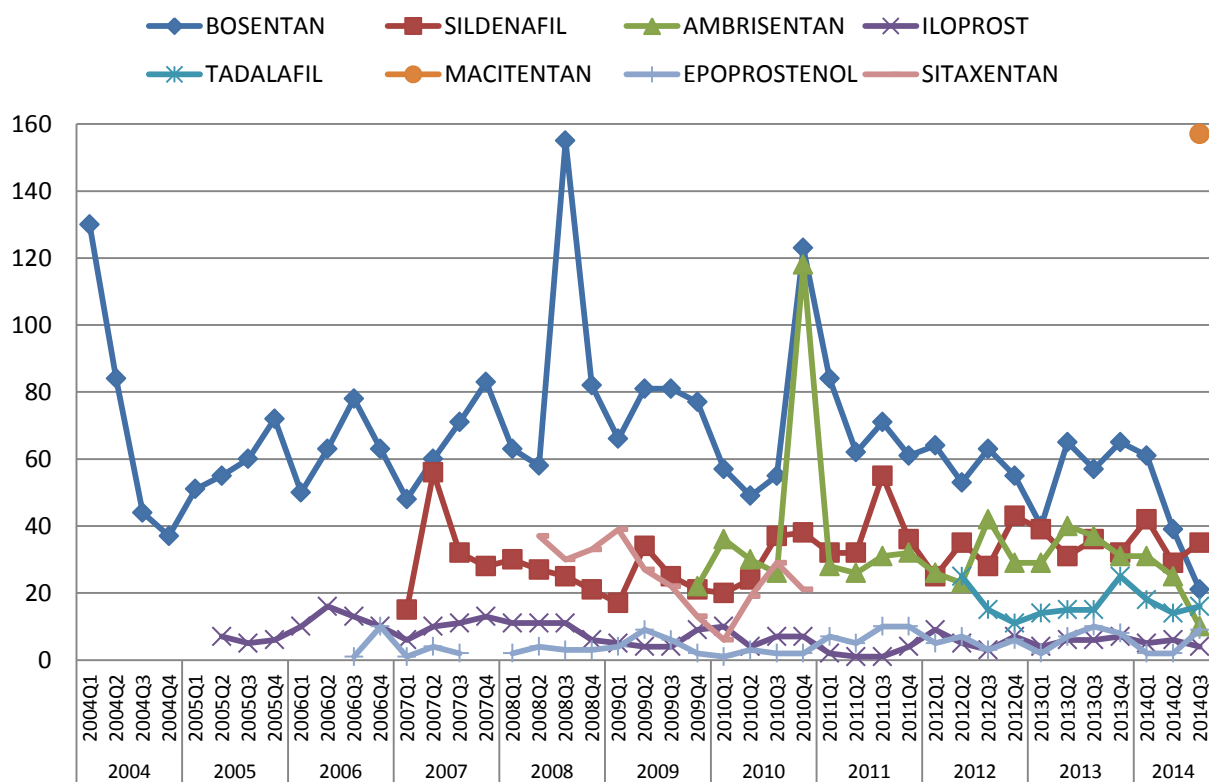
<sup>5</sup> Jansa P, Jarkovsky J, Al-Hiti H, Popelova J, Ambroz D, Zatocil T, et. al. Epidemiology and long-term survival of pulmonary arterial hypertension in the Czech Republic: a retrospective analysis of a nationwide registry. BMC Pulm Med 2014; 14: 45. doi:10.1186/1471-2466-14-45

The large spike in the number of patients initiating PAH therapy on bosentan in 2008 Q3 was associated with the extension of the bosentan listing on 1/8/2008 to include treatment of PAH associated with a congenital systemic-to-pulmonary shunt (including Eisenmenger's physiology). This was recommended at the March 2008 PABC meeting.

It can be seen that patients rarely initiate PAH therapy on iloprost or epoprostenol. This is not unexpected given that other medicines are administered orally and also because iloprost and epoprostenol have been limited since 1/8/2009 in the PBS restriction to patients with advanced disease (i.e. WHO Functional Class IV, see Figure 1), except iloprost can also be used for drug-induced PAH in WHO Functional Class III patients.

Macitentan has become the most common medicine for new patients since it was listed on 1/9/2014. The dominance of the new patient market will be much greater than implied in Figure 3 as the macitentan data point includes only one month of data.

Figure 4 shows initiations to individual PAH medicines, as opposed to Figure 3 which shows the first medicine used in PAH therapy. Patients will be represented multiple times in Figure 4 if they switch PAH medicines.



**Figure 4: Patients - initiating to individual PAH drugs, based on authority approvals**

Source: DHS Authority Approvals database

Note: Macitentan was listed on the 1/9/2014 and so 2014 Q3 only contains one month of data

In 2010 Q4 there were large spikes in the number of patients initiating to bosentan and ambrisentan. This corresponds with the withdrawal from the market of sitaxentan in December 2010. These large spikes were not present in Figure 3 as these initiations are for patients who were on sitaxentan before it was delisted and so these patients are initiating a new drug, but not PAH therapy.

Figure 4 shows that 157 patients initiated macitentan in 2014 Q3 and Figure 3 shows that 71 of these were initiating PAH therapy. Thus 86 patients had previously been on another PAH drug (see Table 3 for more details).

Figure 5 shows the prevalent patients from Figure 2 by the medicine prescribed. Patients may be included in multiple medicines within a year if they switched medicine during the year.

### **Figure 5: Patients – prevalent on PAH drugs, based on authority approvals**

Source: DHS Authority Approvals database

Note: Macitentan was listed on the 1/9/2014 and so 2014 Q3 only contains one month of data

The number of patients on bosentan has plateaued. The drugs with strongest growth of prevalent patients are ambrisentan, tadalafil and macitentan.

Table 3 is an analysis by drug prior to initiation (i.e. the PAH drug approved prior to initiation of another PAH drug) for all initiations shown in Figure 3. Where prior drug is “None”, the initiation to the drug is also an initiation to PAH therapy. Thus in total 4,044 patients have initiated PAH therapy and PAH drugs have been initiated 5,528 times by these patients. If a prior drug exists then the patient has either switched from this drug to

the newly initiated drug, or had a break in treatment with the prior drug and subsequently initiated on the new drug.

**Table 3: Initiating patients by drug initiated and prior drug, based on authority approvals**

Patients drug initiated	Prior drug								Total
	AMBRISENTAN	BOSENTAN	EPOPROSTENOL	ILOPROST	SILDENAFIL	SITAXENTAN	TADALAFIL	None	
AMBRISENTAN	-	186	5	12	41	99	5	324	672
BOSENTAN	23	-	2	9	73	57	5	2,688	2,857
EPOPROSTENOL	13	83	-	16	7	5	1	27	152
ILOPROST	17	143	8	-	27	7	-	64	266
MACITENTAN	24	51	-	-	7	-	4	71	157
SILDENAFIL	36	217	1	22	-	20	3	681	980
SITAXENTAN	5	98	1	10	40	-	-	122	276
TADALAFIL	14	36	-	3	48	-	-	67	168
<b>Total</b>	<b>132</b>	<b>814</b>	<b>17</b>	<b>72</b>	<b>243</b>	<b>188</b>	<b>18</b>	<b>4,044</b>	<b>5,528</b>

% Patients									
AMBRISENTAN	0%	28%	1%	2%	6%	15%	1%	48%	100%
BOSENTAN	1%	0%	0%	0%	3%	2%	0%	94%	100%
EPOPROSTENOL	9%	55%	0%	11%	5%	3%	1%	18%	100%
ILOPROST	6%	54%	3%	0%	10%	3%	0%	24%	100%
SILDENAFIL	15%	32%	0%	0%	4%	0%	3%	45%	100%
TADALAFIL	4%	22%	0%	2%	0%	2%	0%	69%	100%
MACITENTAN	2%	36%	0%	4%	14%	0%	0%	44%	100%
SITAXENTAN	8%	21%	0%	2%	29%	0%	0%	40%	100%
<b>Total</b>	<b>2%</b>	<b>15%</b>	<b>0%</b>	<b>1%</b>	<b>4%</b>	<b>3%</b>	<b>0%</b>	<b>73%</b>	<b>100%</b>

Source: DHS Authority Approvals database, data includes all approvals from 2004 Q1 to 2014 Q3 inclusive.

The 6 most common switches have been;

- from bosentan to sildenafil (217 patients)
- from bosentan to ambrisentan (186 patients)
- from bosentan to iloprost (143 patients)
- from sitaxentan to ambrisentan (99 patients)
- from bosentan to sitaxentan (98 patients)
- from bosentan to epoprostenol (83 patients)

These switches have been influenced by the order of PBS listing, with bosentan being the most commonly switched from drug partly because it was listed first, but also because most patients initiated PAH therapy on bosentan even when the alternative drugs were available (except for the most recent quarter, 2014 Q3, where macitentan was the most common, see Figure 3). The sitaxentan to ambrisentan switches would have been related to the delisting of sitaxentan.

Table 4 shows the distribution of the number of PAH drugs initiated by the 4,044 patients over the period 2004 Q1 to 2014 Q3 inclusive. The PBS restrictions allow switching between PAH drugs and have done so since the listing of iloprost, the second listed PAH drug.

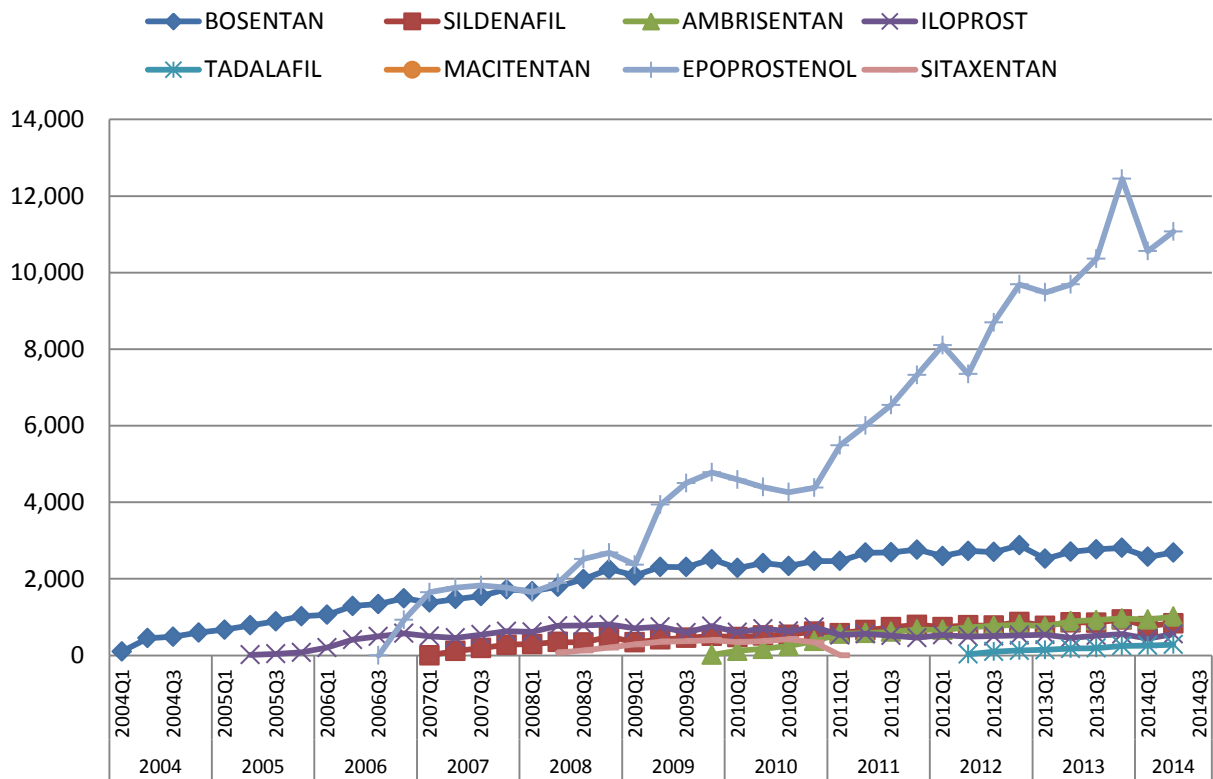
**Table 4: Distribution of number of PAH drugs initiated**

PAH drugs initiated	Patients
1	2951
2	792
3	224
4	64
5	13
Total	4,044

Source: DHS Authority Approvals database, data includes all approvals from 2004 Q1 to 2014 Q3 inclusive.

## Pack and prescription utilisation

Figure 6 shows the number of packs supplied for PAH drugs by quarter of supply.



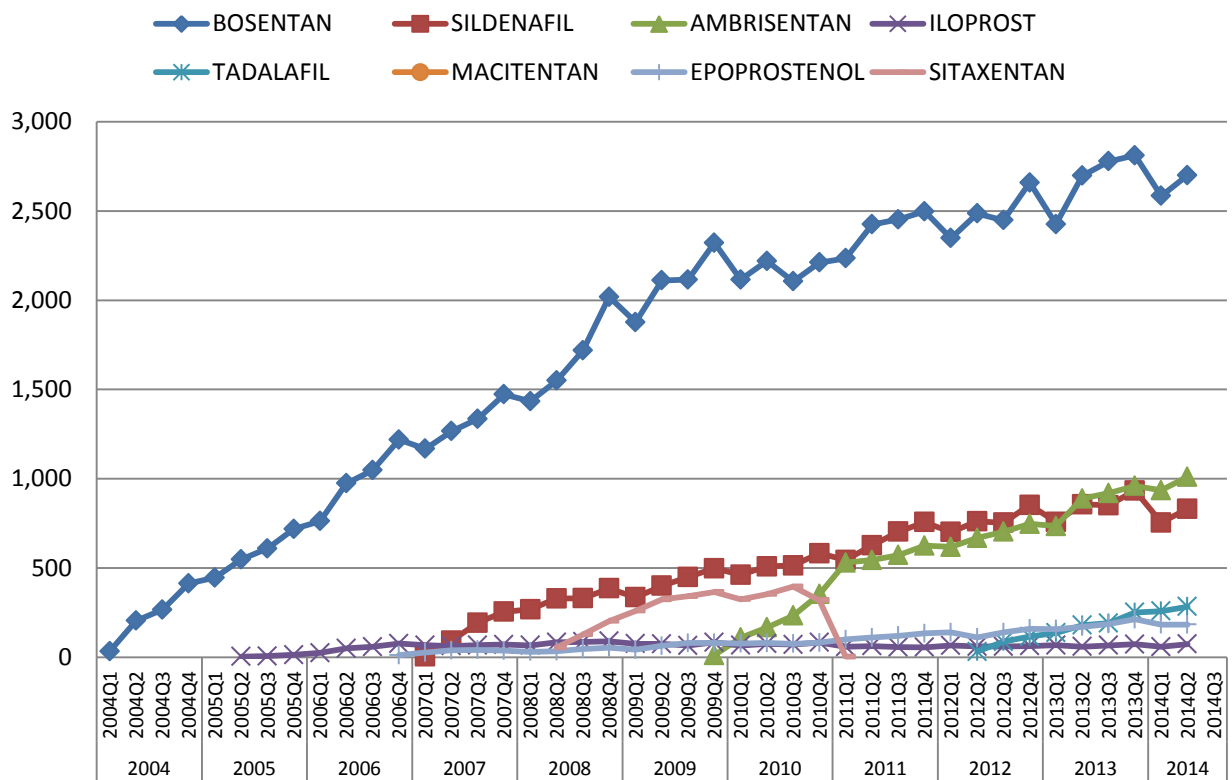
**Figure 6: Packs supplied for PAH drugs by quarter of supply**

Source: DUSC HSD database.

Note that pack supply data shown in Figure 6 was only available until the end of 2014 Q2, whereas the approval data in Figures 2 to 5 was available to 2014 Q3. This is because of the significantly longer lag from pack supply to DHS processing of claims compared to the lag from approval to the approval data being available to the Department of Health. Thus there is no pack data for macitentan which was listed on 1 September 2014.

As the PAH drugs are listed in the s100 Highly Specialised Drugs (HSD) Program, the utilisation measure normally used is packs because prescriptions are not reported for a portion of the data. That is, HSD drugs prescribed in public hospitals and processed via the DHS Offline processing system were only reported as packs and not prescriptions. The problem with Figure 6 is that patients, on average, consume many more packs per month of epoprostenol, than for the other PAH drugs. Thus Figure 6 gives the false impression that epoprostenol is the most highly utilised drug, which appears to be inconsistent with the prevalent patient counts in Figure 5.

Fortunately only a low proportion of PAH drugs were processed via the DHS Offline system (see Appendix B for details), so reporting prescriptions is only a slight under-estimate of utilisation prior to July 2013. The DHS Offline system was phased out in June 2013 and so from this point on prescription utilisation is complete (i.e. no longer a slight underestimate). Figure 7 shows the prescription utilisation by drug.



**Figure 7: Prescriptions supplied for PAH drugs**

Source: DUSC HSD database

The utilisation ranking of the drugs in Figure 7 is now consistent with the prevalent patient count in Figure 5. To elucidate the utilisation of these drugs further, expressing the utilisation in Defined Daily Doses per 1000 population was considered. This was not done as epoprostenol does not have a WHO Defined Daily Dose (presumably because it is a weight dependant continuous infusion).

Table 5 shows prescription utilisation in 2013/14 by prescribing Hospital Type and PBS Item code.

**Table 5: Prescriptions in 2013/14 by prescribing Hospital Type and PBS Item code.**

Drug Name	Hospital Type	PBS code	Form, Strength, Pack Size	Prescriptions
BOSENTAN	Public	5618Q	Tablet 62.5 mg (as monohydrate) 60	481
		5619R	Tablet 125 mg (as monohydrate) 60	8,298
	Private	6429J	Tablet 62.5 mg (as monohydrate) 60	110
		6430K	Tablet 125 mg (as monohydrate) 60	1,988
BOSENTAN Total				10,877
SILDENAFIL	Public	9547L	Tablet 20mg 90	1,886
		9605M	Tablet 20mg 90	3
	Private	9605M	Tablet 20mg 90	1,480
SILDENAFIL Total				3,369
AMBRISENTAN	Public	5607D	Tablet 5mg 30	1,408
		5608E	Tablet 10mg 30	1,716
	Private	9648T	Tablet 5mg 30	213
		9649W	Tablet 10mg 30	487
AMBRISENTAN Total				3,824
ILOPROST	Public	5751Q	Solution for inhalation 20ug (base) in 2mL 30	220
	Private	6456T	Solution for inhalation 20ug (base) in 2mL 30	49
ILOPROST Total				269
TADALAFIL	Public	1308W	Tablet 20mg 56	783
	Private	1304P	Tablet 20mg 56	200
TADALAFIL Total				983
EPOPROSTENOL	Public	5030R	Powder for I.V. infusion 500ug (base) infusion administration set 1	45
		5035B	Powder for I.V. infusion 1.5mg (base) infusion administration set 1	592
	Private	5036C	Powder for I.V. infusion 500ug (base) infusion administration set 1	3
		5042J	Powder for I.V. infusion 1.5mg (base) infusion administration set 1	123
EPOPROSTENOL Total				763
Total				20,085

Source: DHS Supplied prescription database combined with DHS HSD Offline processing data.

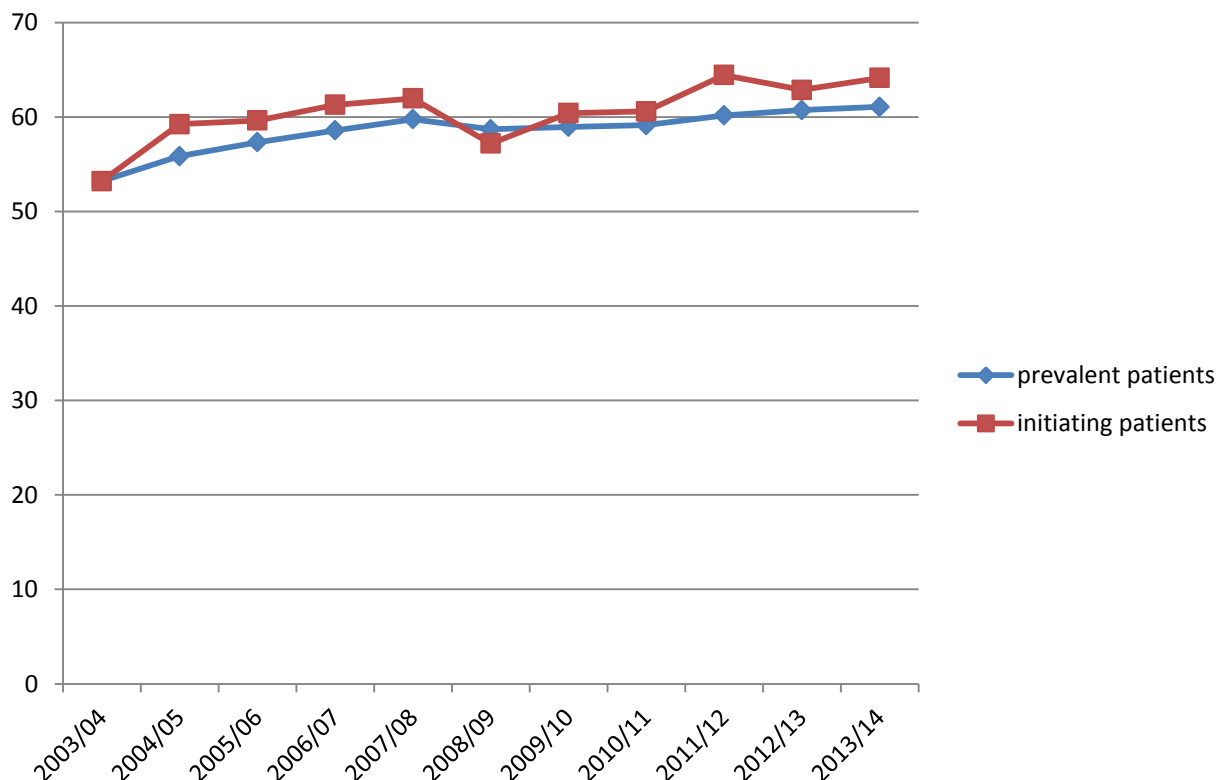
In Table 5 the prescription count is only shown for prescriptions supplied from July 2013 to June 2014 as this is the only period for which the prescription measure of utilisation is 100% complete (as explained above).

To be eligible for PAH medicines, patients must be assessed at a designated hospital. As at 15/12/2014 there were 56 designated centres, including both public and private hospitals, listed on the DHS website<sup>6</sup>.

<sup>6</sup> <http://www.medicareaustralia.gov.au/provider/pbs/drugs2/hypertension.jsp>

## Patient demographics

The mean age of patients initiating PAH therapy has increased slowly over the past decade from 53.2 to 64.1 years (Figure 9). The mean age of prevalent patients has increased from 53.2 to 61.1 years. Figure 9 shows the mean age of incident and prevalent patients by financial year.



**Figure 9: Mean age (years) of incident and prevalent patients by financial year.**

Source: DHS Authority approval and Supplied prescription databases. Age is calculated at first prescription in the period.

Note: The first PAH medicine was listed on 1/3/2004 so 2003/04 only contains 4 months of data.

The mean age of patients in the bosentan arms of the key clinical trial (AC-052-352<sup>7</sup>) was 48.8 years (N = 146, median not reported). This is 15.3 years younger than the mean age of patients initiating PBS PAH therapy in 2013/14. The Bosentan Patient Registry<sup>8</sup> also found that the treated population was generally older than the clinical trial population.

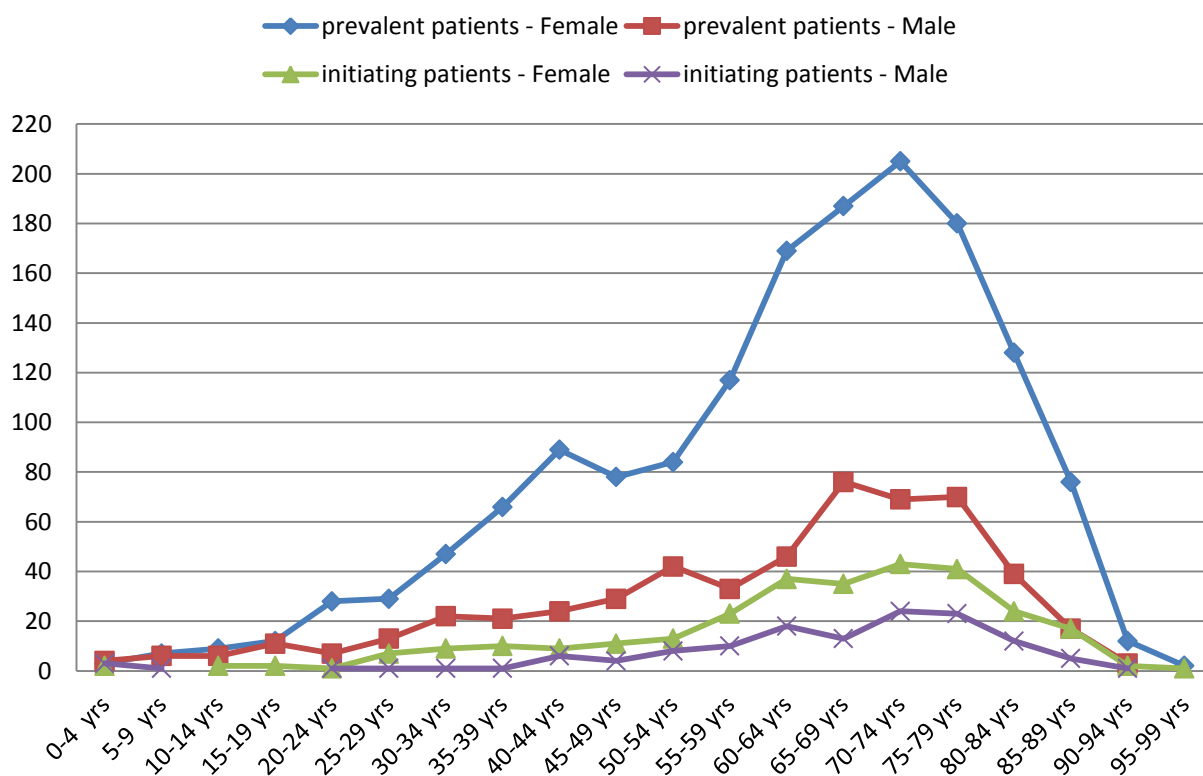
The decrease in mean age of patients receiving their first PBS subsidised PAH medicines in 2008/09 is probably due to the listing of bosentan for pulmonary arterial hypertension associated with a congenital systemic-to-pulmonary shunt (including Eisenmenger's physiology).

<sup>7</sup> Gordon M. MEDICAL REVIEW OF EFFICACY. NDA#21,290. June 29, 2001.

<[http://www.fda.gov/ohrms/dockets/ac/01/briefing/3775b2\\_04\\_efficacy.htm](http://www.fda.gov/ohrms/dockets/ac/01/briefing/3775b2_04_efficacy.htm)>

<sup>8</sup> Keogh A, Strange G, McNeil K, Williams TJ, Gabbay E, Proudman S, et al. The Bosentan Patient Registry: long-term survival in pulmonary arterial hypertension. *Internal Medicine Journal* 2011 Mar;41(3):227-34.

The age distribution of new patients and prevalent patients in the most recent year (2013/14) is shown in Figure 10.



**Figure 10: Incident and prevalent patients by age and gender breakdown for authorities approved for any PAH medicine in the 2013/14 financial year.**

Source: DHS Authority approval and Supplied prescription databases. Age is calculated at first prescription in the period.

Figure 10 shows that PAH patients cover the full age spectrum and there are more female patients (1,528 = 74%) than males (538 = 26%). The gender distribution is consistent with published international prevalence and incidence figures. Peacock et al.<sup>9</sup> reported a 69.8% female and 30.2% male patient split for incident patients in Scotland. Jansa et al.<sup>5</sup> reported 65.9% and 65.0% female patients in the incident and prevalent populations respectively for the Czech Republic. Treatment of anorexigen-induced PAH may be one factor contributing to a higher prevalence in women. Incidence of anoxerigen-induced PAH could reasonably be expected to decline over time. The PBS dispensing data does not capture use by PAH clinical subclass.

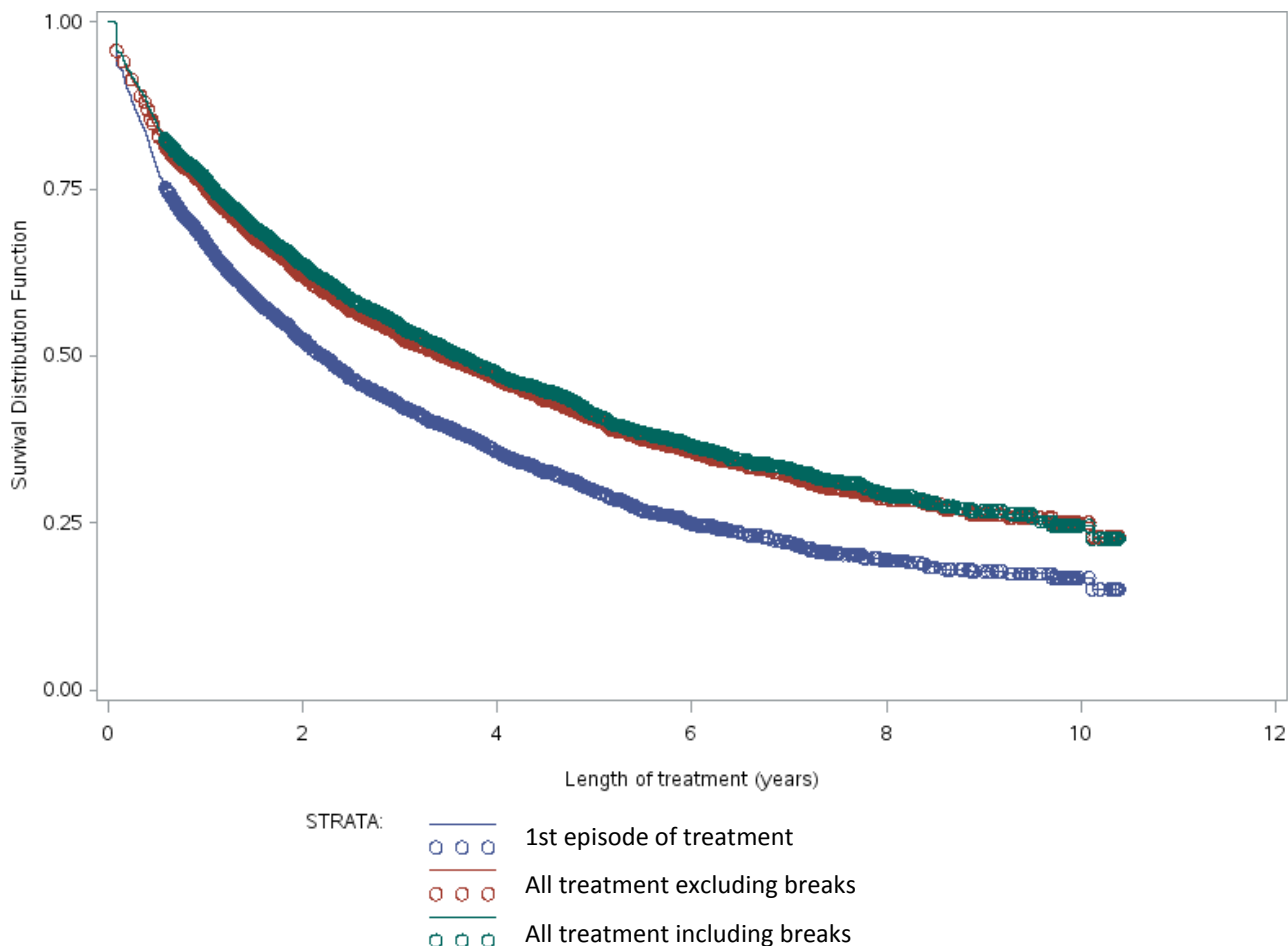
### Length of treatment analysis

This analysis was undertaken to measure the PBS length of treatment and compare this with;

<sup>9</sup> Peacock AJ, Murphy NF, McMurray JJ, Caballero L, Stewart S. An epidemiological study of pulmonary arterial hypertension. *Eur Respir* 2007, 30:104–109.

- that assumed in the recommended bosentan submission to the December 2013 PBAC; and
- that calculated from the Bosentan Patient Registry (BPR) data.

Figure 11 shows length of treatment for first treatment episode and all treatment episodes, the latter with and without accounting for breaks in treatment.



**Figure 11: Length of PAH treatment using various measures**

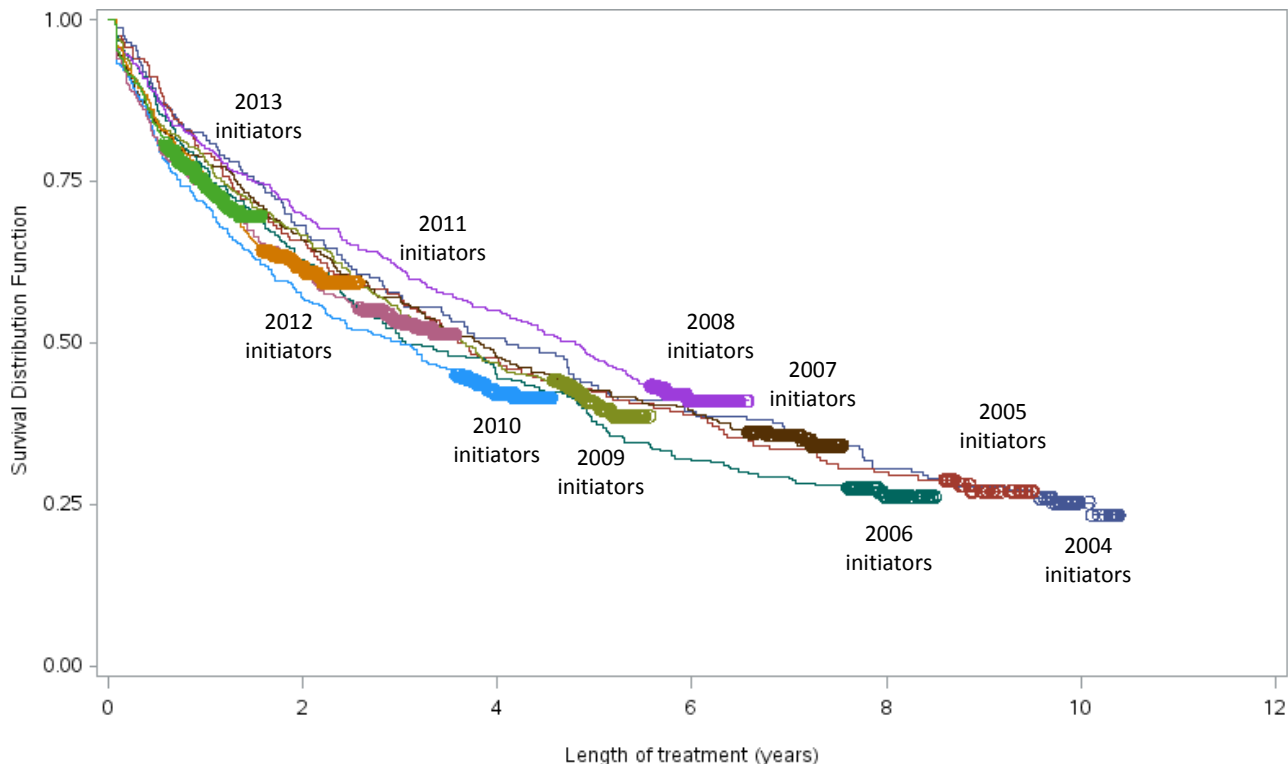
Note: A circle symbol indicates a patient who is deemed to be continuing treatment at the end of the data period.

Source: DHS PBS supplied prescription database for prescriptions supplied from March 2004 to July 2014 inclusive.

The Kaplan Meier (KM) analysis used to produce Figure 11 was also used to estimate median and mean lengths of treatment for the three different measures. The estimated median lengths of treatment were 2.22, 3.45 and 3.66 years for first episode, all excluding breaks and all including breaks respectively. The estimated mean lengths were 3.69, 4.63 and 4.72 years for first episode, all excluding breaks and all including breaks respectively. The number of patients included in the analysis was 3,489. This is the number of PAH treatment initiators in the DHS PBS supplied prescription database from March 2004 to December 2013 inclusive. Patients who initiated treatment in 2014 were excluded from the analysis due to the short length of follow-up (i.e. to July 2014).

The patient continuation rate used in the Section E spreadsheet of the bosentan submission recommended by the PBAC at its December 2003 meeting was derived from the economic model and implied a median length of treatment of approximately 5 years. The median length of all treatment (including breaks) calculated in this analysis (i.e. 3.66 years) is less than this estimate.

Figure 12 shows the length of treatment for yearly cohorts of initiators to PAH therapy.



**Figure 12: Length of all PAH treatment including breaks by year of initiation**

Note: A circle symbol indicates a patient who is deemed to be continuing treatment at the end of the data period. The year cohorts are identified by a label near the continuing patients (i.e. circle symbols).

Source: DHS PBS supplied prescription database for prescriptions supplied from March 2004 to July 2014 inclusive.

Figure 12 shows that patients who initiated in 2008 had the longest median length of treatment (4.80 years). This may be due to extension of the bosentan listing on 1/8/2008 to include treatment of PAH associated with a congenital systemic-to-pulmonary shunt (including Eisenmenger's physiology). Figure 2 shows that there was a large increase in the number of patients initiating PAH therapy in 2008. In 2008 Q3 the number of initiators to PAH therapy approximately doubled compared to previous quarters (see Figure 3). There is some evidence that patients with Eisenmenger's syndrome have a better prognosis<sup>10,11,12</sup>

<sup>10</sup> Hopkins WE, Ochoa LL, Richardson GW, Trulock EP. Comparison of the hemodynamics and survival of adults with severe primary pulmonary hypertension or Eisenmenger syndrome. *Heart Lung Transplant.* 1996;15(1 Pt 1):100.

<sup>11</sup> Hopkins WE. The remarkable right ventricle of patients with Eisenmenger syndrome. *Coron Artery Dis.* 2005;16(1):19.

<sup>12</sup> D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med.* 1991;115(5):343.

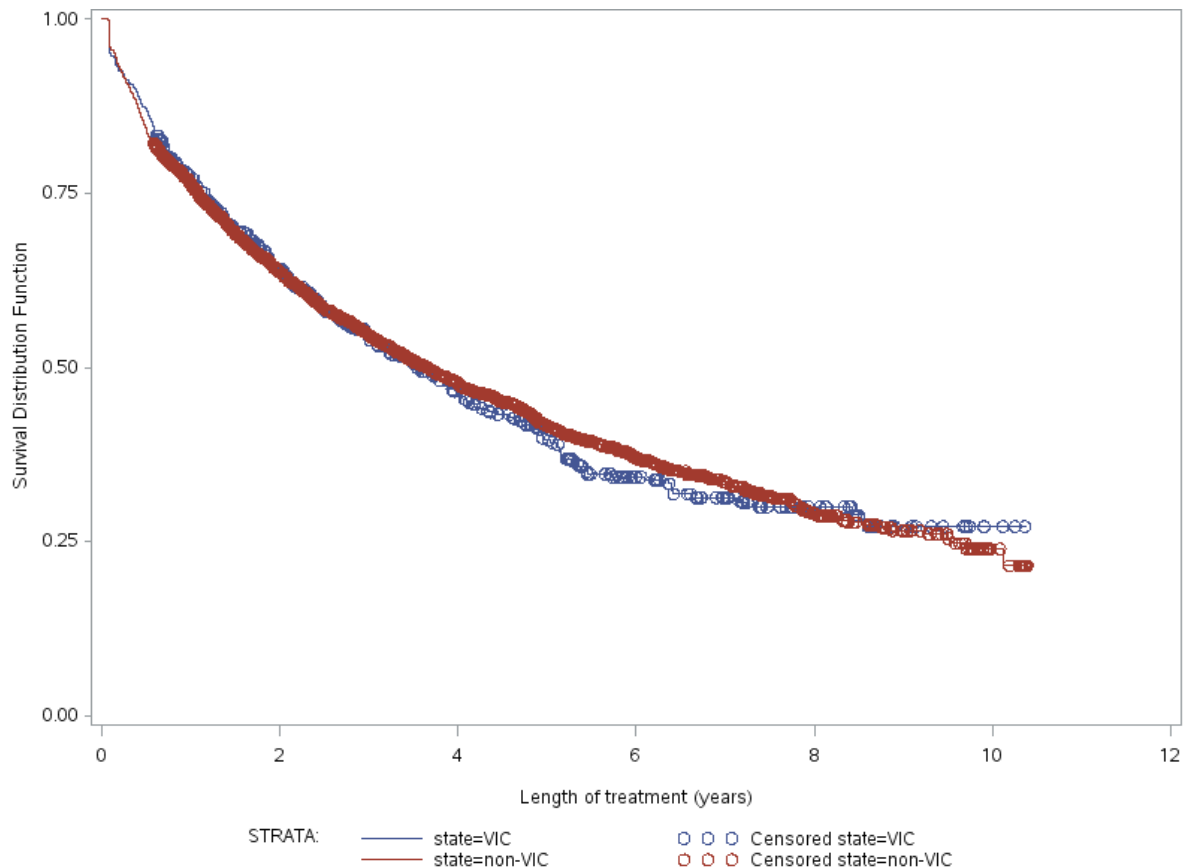
than other PAH patient types and this may account for the increased length of treatment of the 2008 cohort. To confirm this interpretation, it was considered to use the authority approval restriction codes to discern the PAH type at initiation and then re-do the length of treatment analysis by PAH type (e.g. WHO Function Class III or IV, iPAH, anorexigen-induced PAH and hereditary PAH, PAH secondary to connective tissue disease or PAH associated with a congenital systemic-to-pulmonary shunt (including Eisenmenger's physiology) instead of year of initiation. However this was not possible as the restriction codes are not specific enough to enable discrimination between these types.

The cohort with the second longest median length of treatment (4.10 years) was the 2004 initiators. This may be due to the healthy survivor effect that would have affected the first initiators after PBS listing (i.e. patients who initiated on non-PBS bosentan prior to 2004 and were grandfathered onto PBS bosentan in 2004).

The tails of the Survival Distribution Function (SDF) plots in Figure 12 should be interpreted with care. Where the end of the plots becomes horizontal, the SDF is a slight overestimate. This is because, by definition, all the patients with the longest possible length of treatment have their final prescription close to the end of the data period (i.e. 31 July 2014) and so are deemed to be continuing treatment (i.e. "censored"). The Kaplan Meier SDF overestimates if a string of "censored" observations are not interrupted by a "non-censored" one (i.e. one where the patient is deemed to have stopped treatment). This is because the SDF only decreases (i.e. the plot has a step down) when a "non-censored" observation is encountered.

One concern with the methodology of the above KM analyses was that the incomplete patient level data for HSD drugs prior to July 2013 (see Appendix C for details) might lead to an under-estimate of length of treatment for patient who initiated prior to this. This possibility was tested by comparing Victorian patients with non-Victorian patients. The patient level data for Victoria is complete all the way back to the listing of bosentan in March 2004. Thus the comparison may reveal a bias in the method for the non-Victorian patients.

Figure 13 shows length of all PAH treatment (including breaks) for Victorian patients compared to patients from other States.



**Figure 13: Length of all PAH treatment including breaks by VIC vs non-VIC**

Note: A circle symbol indicates a patient who is deemed to be continuing treatment at the end of the data period. Source: DHS PBS supplied prescription database for prescriptions supplied from March 2004 to July 2014 inclusive.

Figure 13 shows that there does not appear to be a difference between the lengths of treatment between the two groups. The Log-Rank test for equality over strata gave non-statistically significant differences between the SDFs ( $p=0.8084$ ). This increases confidence in the results reported in Figures 11 & 12 which includes patients from all states.

*Comparison of length of treatment analysis with results from the Bosentan Patient Registry (BPR)<sup>8</sup>*

The BPR analysis contains 821 patient years of follow-up on 528 patients treated with bosentan in Australia between March 2004 and September 2007 (i.e. up to 3 years and 7 months of follow-up).

The Kaplan Meier (KM) mortality estimate at year 1 after initiating treatment was 12.6% and at year 2 was 26.0%. This compares to KM estimates from Figure 11 of stopping treatment (i.e. All treatment including breaks) at year 1 = 23.3% and at year 2 = 36.1%. The rate of stopping PAH drug therapy is higher than the mortality rate.

When the length of treatment analysis is limited to those who initiated in 2004 to 2007, which corresponds to the period of the BPR operation, then the probability of stopping treatment at year 1 was 21.3% and at year 2 was 34.7%.

Length of exposure was reported in the BPR analysis using a mean, but not using KM median or survival estimates. Exposure to bosentan was up to 6.6 years (for grandfathered patients) with a mean exposure of 2.1 years. This report used data from the period March 2004 to July 2014 (i.e. up to 10 years and 5 months of follow-up, but no regard to length of treatment pre-PBS listing). The mean length of treatment on PAH drug therapy (i.e. not limited to bosentan) was 4.72 years (including breaks in therapy, which matches the definition used in the BPR analysis). This difference in mean exposure may simply be due to the difference in the length of follow-up. Mean exposure is sensitive to length of follow-up whereas KM median exposure (or KM probability of stopping at 1 or 2 years) is relatively insensitive to the length of follow-up.

A potential problem with the above comparison is that iloprost, epoprostenol and sildenafil were all listed during the period of the registry operation and switching to these products may have shortened the mean exposure to bosentan reported in the Statistical Analysis Report for BPR.

### **Estimated prescribed dose**

The DUSC has previously questioned the doses of epoprostenol, therefore the doses of epoprostenol have been investigated further in the current report.

Epoprostenol was recommended for listing on a cost-minimisation basis to bosentan for WHO Class III or IV patients with primary PH. The equi-effective doses defined by the PBAC were epoprostenol, commencing at an average dose of 11.9 ng/kg per minute (continuous infusion) over the first three months of treatment and escalating linearly in steps to an average dose of 27.2 ng/kg per minute at 3 years, and bosentan 125 mg twice a day.

To assess whether the equi-effective doses have been maintained in practice it is necessary to translate the dose for epoprostenol from ng/kg/minute into mg/day. To do this an average body weight needs to be assumed. In 2011-12 the average weights of Australian men and woman were 85.9kg and 71.1kg respectively<sup>13</sup>. The proportion of men and women treated with PAH drugs in 2013/14 was 26% and 74% respectively. Assuming these patients are of average weight the weighted average patient weight was 74.9kg.

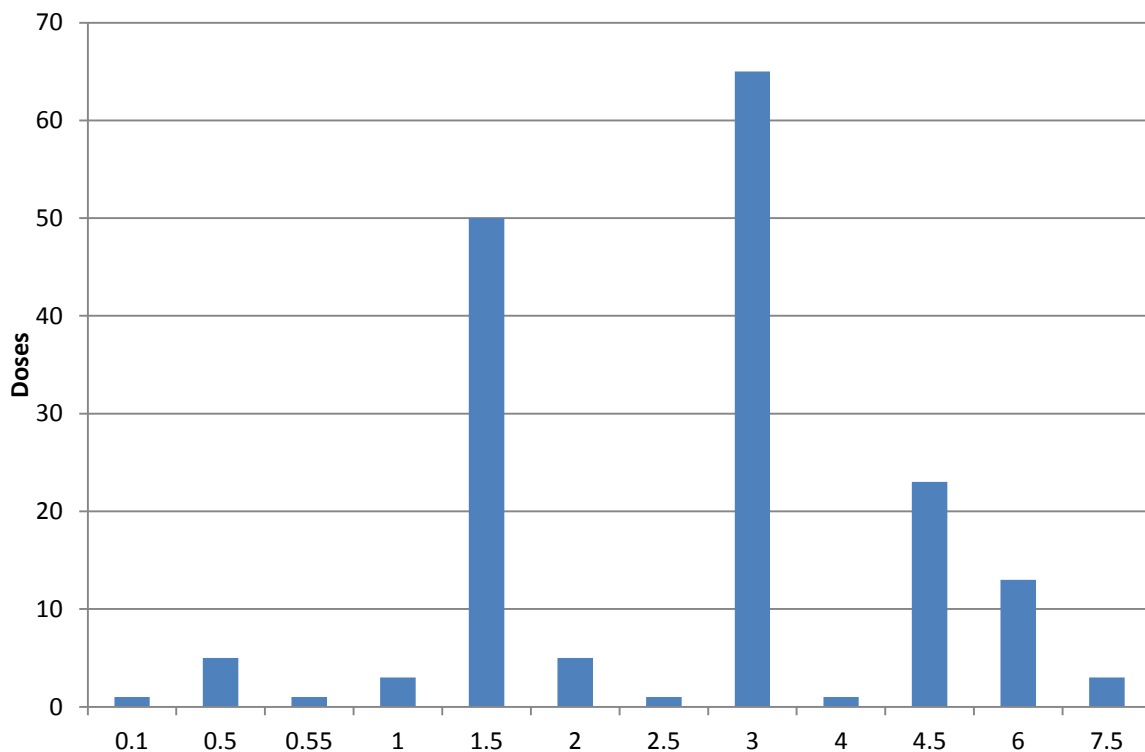
The dose escalation of 11.9 ng/kg per minute (continuous infusion) over the first three months increasing linearly in steps to an average dose of 27.2 ng/kg per minute at 3 years, results in a weighted average dose over 3 years of 18.9 ng/kg per minute. This translates to a dose of;

18.9 ng/kg per minute x 74.9kg x 60 minutes/hour x 24 hours = 2.04 mg/day.

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<sup>13</sup> 4338.0 - Profiles of Health, Australia, 2011-13 , Australian Bureau of Statistics publication

Figure 14 shows the estimated daily dose of epoprostenol derived from the Authority Approvals data for the 13/14 financial year. See Methodology section for further details.

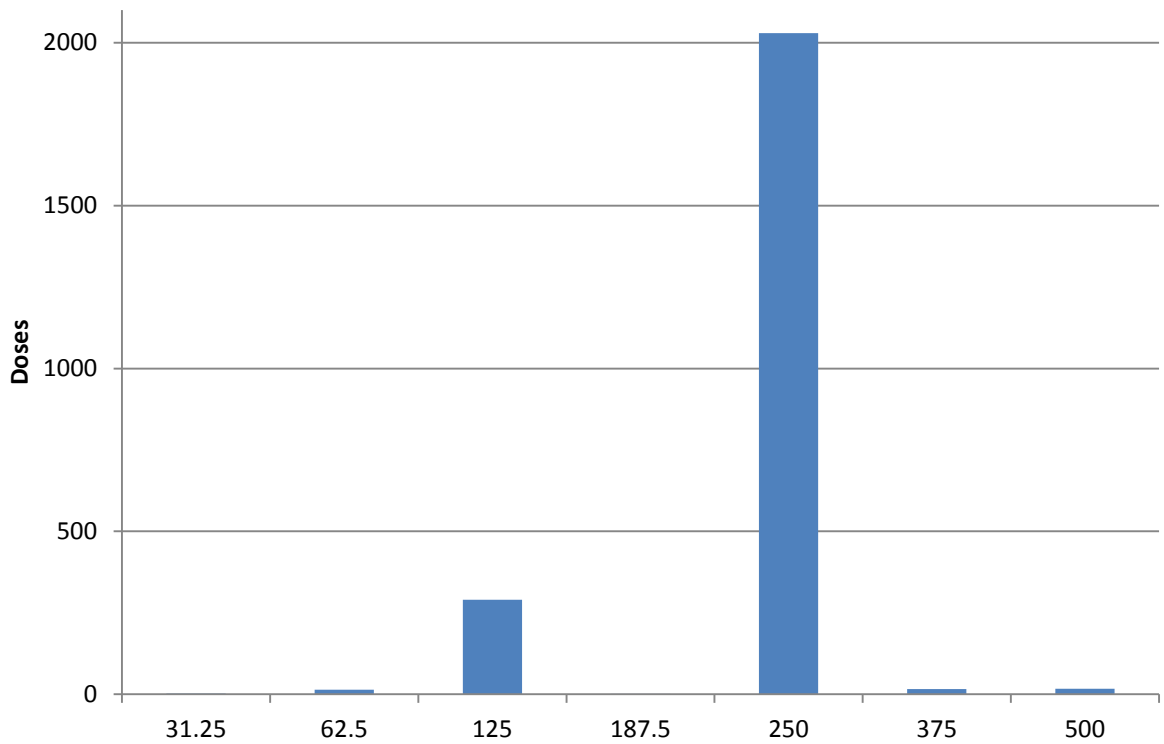


**Figure 14: Distribution of epoprostenol estimated daily dose (mg/day)**

Source: DHS Authority Approvals database, approvals in the 2013/14 financial year

The weighted average dose of all doses in Figure 14 is 2.90 mg/day, which is 42% more than the PBAC equi-effective dose.

For completeness, the distribution of bosentan doses is provided in Figure 16. The recommended dosage in the bosentan product information is “initially 62.5 mg twice daily for 4 weeks. Increase to a maintenance dose of 125 mg twice daily. Doses above 125 mg twice daily did not appear to confer additional benefit sufficient to offset the increased risk of liver injury.”



**Figure 15: Distribution of bosentan estimated daily dose (mg/day)**

Source: DHS Authority Approvals database, approvals in the 2013/14 financial year

The most common dose of bosentan is 250 mg per day, which is consistent with the dose of bosentan used to establish equi-effective doses with epoprostenol.

## Analysis of expenditure

Table 6 shows combined Repatriation PBS (ie. Department of Veterans Affairs) and PBS (R/PBS) expenditure by financial year

**Table 6: R/PBS expenditure by financial year (date of supply, published prices)**

Financial Year	R/PBS Published Expenditure (\$ Million)
2004/05	\$8.4M
2005/06	\$14.4M
2006/07	\$19.8M
2007/08	\$24.9M
2008/09	\$34.5M
2009/10	\$48.4M
2010/11	\$56.3M
2011/12	\$62.2M
2012/13	\$65.8M
2013/14	\$54.2M
<b>Total</b>	<b>\$388.9M</b>

Some medicines have special pricing arrangements, and government expenditure may be less than presented. There was a change in one of these arrangements in 2013/14 accounting for the apparent expenditure reduction.

Bosentan, ambrisentan and iloprost have Special Pricing Arrangements.

## Discussion

The first medicine specifically for PAH was listed on the PBS in 2004. Since then 7 further medicines, from three different pharmacological classes, have become available through the PBS. From 2004 to 2007 approximately 300 new patients each year started treatment with a PAH therapy. This increased in 2008 following a broadening of the restriction to include PAH associated with congenital systemic-to-pulmonary shunts, and has since remained steady at approximately 400 new patients per year. Bosentan was the most commonly prescribed first PAH medicine until very recently. Macitentan, listed on the PBS from September 2014, is now the most frequently prescribed first medicine. Patients commencing PAH therapy in Australian clinical practice are on average older than those in the key clinical trials, and the average age at initiation has increased by five years between 2004 and 2014.

The total number of people on treatment has been increasing over time. Compound annual growth in the prevalent population was 37% between 2004 and 2009. Although still increasing, the rate of growth has declined to about 7% in recent years. This indicates that patients are remaining on treatment for long durations. In this report, the median length of

the first episode of PAH treatment was estimated to be 2.22 years. The total median length of treatment, including switches to other medicines and breaks in therapy was 3.66 years. Patients are allowed to switch or use medicines sequentially if they meet the PBS criteria and have not previously failed treatment with the particular agent. Of 4,044 patients starting PAH treatment between 2004 and 2014, about 27% have progressed to a second agent, 5% to a third agent, and less than 2% to a fourth or fifth agent. There appears to be switching within pharmacological classes when new products become available. For example switching from bosentan to sitaxentan, ambrisentan or macitentan. However the majority of changes in therapy are to alternate classes, presumably due to lack of response.

The dose of epoprostenol used in practice appears to be substantially higher than that used as the basis for equi-effective dose against bosentan. Although it is recognised that dose determination is difficult where the dose is gradually increased over a long duration, and that patients treated with epoprostenol may have more severe disease than patients on oral medicines, the cost-effectiveness of these higher doses is not known.

The data collected through the authority approval system has enhanced the analyses in this report, particularly because patient level PBS prescription data was incomplete prior to mid-2013. Although not captured in the data available to the Secretariat, the DHS may have additional information, such as the clinical classification subcategory, that could be requested to further understand use of PBS subsidised PAH medicines. Another parameter of interest may be the proportion of approvals that are based on RHC and/or ECHO, and if this has changed over time. At the time of recommending bosentan for listing, the PBAC stated that the restriction should take into account that diagnosis via right heart catheter is the most desirable, followed by ECHO and then the six minute walk test. These types of information may also be available from the PHSANZ PHT patient registry.

The data in this report did not indicate that PAH medicines have been used beyond the PBS restrictions. As there is some discordance between PBS criteria and clinical guidelines<sup>3</sup> there is some risk of use outside of PBS criteria. This may include treatment of functional class II patients with endothelin receptor antagonists, or use of combination therapy. The PHSANZ has highlighted differences between guidelines and PBS restrictions in their correspondence to PBAC but the PBAC has noted that determining the cost-effectiveness of these indications would require a submission to the PBAC. There is also potential use outside of restriction for other PH classifications for which there are no subsidised options currently available. For example, chronic thromboembolic pulmonary hypertension.

The DUSC considered it important to be cognisant when interpreting the results that switching from sitaxentan was not due to failure or preference, but a result of this medicine being withdrawn from the market.

The DUSC considered that:

- The increasing prevalence of patients on PAH treatment (Figure 2) is a reflection of the increasing survival of these patients;
- The PBS restriction is not consistent with current treatment guidelines in that;

- it requires failure to respond to 6 or more weeks of appropriate vasodilator treatment for WHO Functional Class III patients with a mean right atrial pressure of 8 mmHg or less;
  - it does not allow treatment of functional class II patients; and
  - it does not allow combination therapy.
- As previously stated by the PBAC, changes to the PBS restriction to allow
    - combination therapy;
    - treatment of WHO Functional Class II patients; and /or
    - changes to the discontinuation and switching of medications criteria;
 will require a submission consistent with the requirements outlines in the Guidelines for preparing submissions to PBAC. The DUSC considered that registry data could be an informative part of a submission. The DUSC considered that high quality registry data, if available, may be informative
  - The DUSC noted that in practice, combination therapy is achieved by adding low cost private prescription sildenafil to another of the PBS subsidised drugs.
  - The reason for the gradual increase in the age of incident patients is not known, but may reflect that with increased real world experience, physicians are more comfortable treating older patients.

#### Modification of PBS restriction

The PHSANZ had previously requested the removal of the PBS requirement for WHO Functional Class III patients with a mean right atrial pressure of 8 mmHg or less to trial calcium channel blockers as it is not evidence based.

The DUSC considered that the PBAC could now reconsider whether this requirement remains appropriate. The DUSC did not consider that this minor change would increase the use or costs of PAH medicines.

#### Estimated prescribed dose of epoprostenol

The sponsor of epoprostenol commented on the analysis of average prescribed dose of epoprostenol and the issues raised are dealt with in the DUSC minutes. They also pointed that epoprostenol is PBS listed for WHO functional class III patients who have failed to respond to a 2nd-line option. The report had incorrectly stated that “On 1/8/2009 the listing was limited to WHO Functional Class IV patients”. However this statement is only true in regard to initiating patients. This error has been corrected in this Public Release document.

The DUSC considered that, even though the report found that the actual dose of epoprostenol is greater than that assumed by the PBAC at the time of listing, this is not a large issue as the utilisation of epoprostenol is relatively small (see Figures 5 and 7).

## **DUSC actions**

- The DUSC requested that the report be provided to the PBAC.
- The DUSC recommended that the PBAC consider removing the requirement for a “patient to have failed to respond to 6 or more weeks of appropriate vasodilator treatment unless intolerance or a contraindication to such treatment exists” from the PBS restriction.

## **Context for analysis**

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

## **Sponsors’ comments**

- Actelion Pharmaceuticals Australia Pty Ltd - bosentan, epoprostenol, macitentan
- Bayer Australia Ltd - iloprost
- GlaxoSmithKline Australia Pty Ltd – ambrisentan, epoprostenol
- Apotex Pty Ltd – sildenafil
- Pfizer Australia Pty Ltd – sildenafil
- Eli Lilly Australia Pty Ltd – tadalafil

There were no comments from the sponsors.

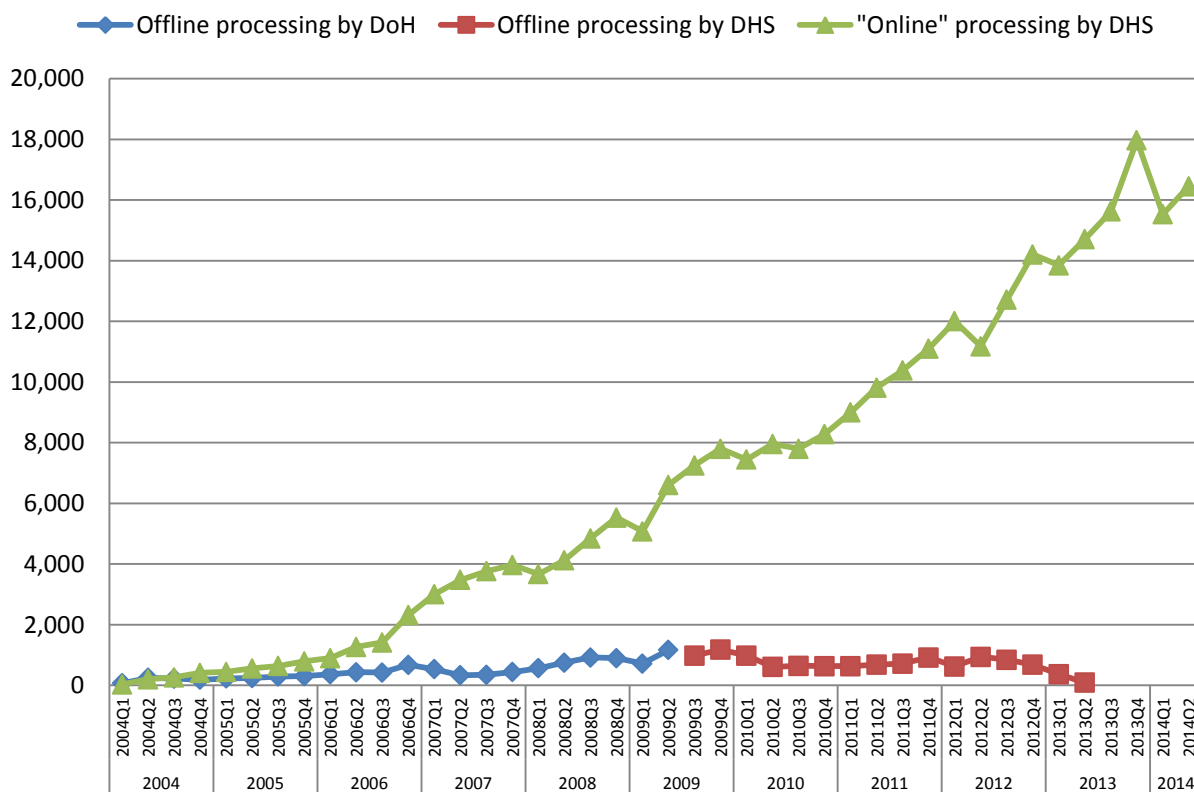
## Appendices

### Appendix A: TGA indications

PAH drug	TGA approved indications
bosentan	<ul style="list-style-type: none"> <li>• idiopathic pulmonary arterial hypertension</li> <li>• familial pulmonary arterial hypertension</li> <li>• pulmonary arterial hypertension associated with scleroderma or</li> <li>• pulmonary arterial hypertension associated with congenital systemic to pulmonary shunts including Eisenmenger's physiology</li> </ul> in patients with WHO functional Class II, III or IV symptoms
iloprost	Treatment of patients with primary pulmonary hypertension or secondary pulmonary hypertension due to connective tissue disease or drug-induced, in moderate or severe stages of the disease. In addition, treatment of moderate or severe secondary pulmonary hypertension due to chronic pulmonary thromboembolism, where surgery is not possible.
epoprostenol	long-term treatment, via continuous intravenous infusion, in WHO functional class III or class IV patients with: <ul style="list-style-type: none"> <li>• Idiopathic pulmonary arterial hypertension</li> <li>• Familial pulmonary arterial hypertension</li> <li>• Pulmonary arterial hypertension associated with the scleroderma spectrum of diseases</li> </ul> Note: This information is from the FLOLAN® for Injection PI, there was a second brand (Veletri®) listed on the PBS on 1/8/2014. It is indicated for the same conditions.
sildenafil	treatment of patients with pulmonary arterial hypertension classified as WHO functional classes II and III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease. The efficacy has not been established in patients currently on bosentan therapy.
sitaxentan	Delisted and no PI available.
ambrisentan	treatment of: <ul style="list-style-type: none"> <li>• idiopathic pulmonary arterial hypertension (PAH),</li> <li>• pulmonary arterial hypertension associated with connective tissue disease (PAH-CTD),</li> </ul> in patients with WHO functional class II, III or IV symptoms.
tadalafil	in adults for the treatment of pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease.
macitentan	as monotherapy or in combination with approved PAH treatments (phosphodiesterase-5 inhibitors or inhaled prostanoids), is indicated for the treatment of: <ul style="list-style-type: none"> <li>• idiopathic pulmonary arterial hypertension</li> <li>• heritable pulmonary arterial hypertension</li> <li>• pulmonary arterial hypertension associated with connective tissue disease</li> <li>• pulmonary arterial hypertension associated with congenital heart disease with repaired shunts in patients with WHO Functional class II, III or IV symptoms.</li> </ul>

## Appendix B: Further details on methodology

### Processing methods for PAH medicine supplies

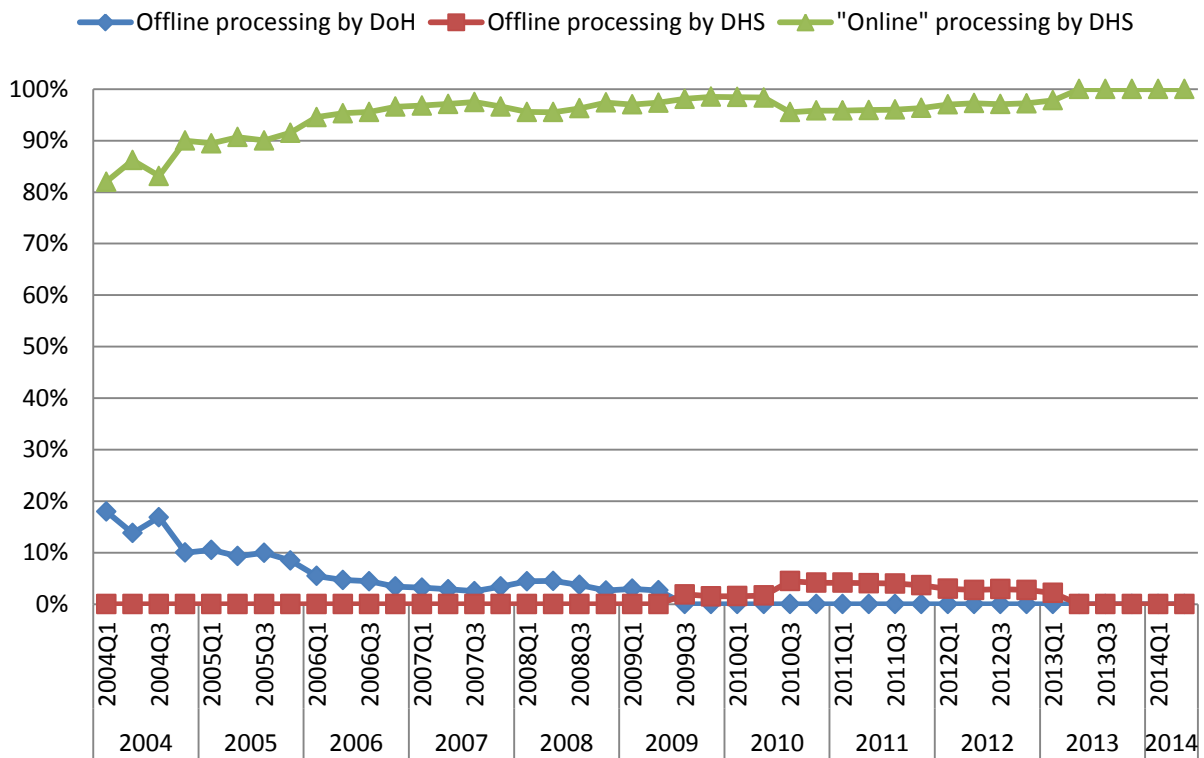


**Figure D.1: Packs supplied for PAH drugs by processing method**

Source: DUSC HSD database

Packs processed via the “Online” method are also reported as prescriptions and each prescription has a patient specific number which enables patient level analysis (e.g. length of treatment).

Figure D.2 shows the data in Figure D.1 as a percentage of packs by processing method. It can be seen that the “Online” by DHS method reaches 100% in 2013 Q3 also Offline process was phased out in June 2013. Also the percentage of “Online” processed packs is around 90% from 2007 Q2. This means that length of treatment analysis can for performed from this date, but the result will be a slight underestimate as it is possible that a patient’s prescription would be missing (i.e. processed via the Offline system) from the patient level prescription data. The likelihood of a missing prescription would be less than 10% however because a patient who has some prescriptions in an environment that has prescriptions processed “Online” (ie. private hospitals and some public hospitals) is relatively unlikely to switch to an environment that processes prescription offline (i.e. the remaining public hospitals).



**Figure D.2: % Packs supplied for PAH drugs by processing method**

Source: DUSC HSD database

Alternatively, length of treatment analysis could be done for patients in the state of Victoria only as 100% of packs processed for patients in Victoria have been processed via the "Online" system since 2004 Q1. This means the prescription history for these patients would be complete (unless the patient moved state).

A further alternative for estimating length of treatment would be to use authority approval data as this also contains the patient specific number required for patient level analysis. However this would be less accurate than using prescription data as there is a longer time between authorities than prescriptions. The advantage of using authority approval data would be that it is complete for patients in all states and across the entire time period.

### ***Method for counting the number of patients treated***

The number of prevalent patients was determined by counting the number of person specific numbers (non-identifying) in the authority approval data for the specified time period. New (initiating) patients were defined as those with no prior PBS or RPBS authority approval for the drug or drug group of interest.

The patients were counted from the authority approvals data and not the DHS prescription claim data as the latter is incomplete with respect to patient level supply history for highly specialised drugs prior to July 2013 (see Appendix A for an analysis of the completeness of this data). This is because some HSD prescriptions were processed via the DHS Offline processing system which does not provide a person specific number. A disadvantage of using authority approval data compared to supplied prescription data for counting prevalent patients is that approvals are less frequent than prescriptions. This means that whilst the supplied prescription data would be expected to capture nearly all prevalent patients in a 3 month period from prescriptions that are normal supplied monthly, this would not be the case for approvals that are only required every 6 months (i.e. the 3 month prevalence estimated from approvals would be a large underestimate of the true prevalence).

In Appendix C the Number of Repeats is 0 for all the PAH item listings. This means that the prescriber has to specify the Number of Repeats when requesting the approval. Analysis of the approval data for this group of drugs shows that the most common number of repeats approved is five. The median time to re-supply of prescription was calculated as part of the length of treatment analysis in this report. The median times to re-supply by drug are reported in this Appendix (See next section "Detailed methodology for Kaplan Meier length of treatment analyses"). The longest median time to resupply is 37 days for iloprost. This means that to capture all prevalent patients in the data, given that most have one original and five repeats, the period over which prevalence needs to be calculated is greater than 6 months. Thus in this report prevalence is calculated over a period of a year to avoid underestimation. Incidence however is not affected by the above problem (i.e. it can be calculated accurately for any period length) and so is calculated quarterly for the initiating patients by drug analysis (see Figure 3 & 4) to show the temporal effects of listing changes on initiations.

### **Detailed methodology for Kaplan Meier length of treatment analyses**

A break in treatment is defined as a gap of 2 x Standard Coverage Days (SCD) in drug coverage which is equivalent to 3 x SCDs between prescription supply. An episode is defined as the time from the first prescription to the last prescription before a break plus one SCD (ie. the coverage of the last prescription). The prescription after a break in treatment is defined as the first prescription of the next episode. The SCDs are equal to the median time to re-supply of prescriptions calculated at the drug level. The table below shows the SCDs used in this analysis.

<b>Drug</b>	<b>Median time to re-supply by any item of the specified drug = SCD (days)</b>
bosentan	30
iloprost	30
epoprostenol	29
sildenafil	37
sitaxentan	31
ambrisentan	30
tadalafil	28
macitentan	NA

The data period used in the length of treatment analysis was from March 2004 (the listing of bosentan for PAH) and July 2014 inclusive. A patient was deemed to be continuing treatment (ie. censored for the purposes of the KM analysis) at the end of the data period if the supply of their last prescription was within 3 x SCDs (which is equivalent to the item coverage end date being within 2 x SCDs) of the end of the data period (ie. 31 July 2014). Patients initiating between January and July 2014 inclusive are excluded as they have minimal follow-up time. Three lengths of treatment were calculated, ie. the length of;

- the first episode of treatment (ie. up to the first break in treatment);
- all treatment excluding breaks (ie. the sum of all episodes); and
- all treatment including breaks (ie. the time from the first prescription of the first episode to the last prescription of the last episode plus one SCD (ie. the coverage of the last prescription)).

When two different strengths (ie. PBS items) of the same drug were supplied on the same day it was assumed that these strengths were taken concurrently (ie. were necessary to achieve the prescribed dose). This is not considered stockpiling.

### **Stockpiling**

In previous KM analyses performed by DUSC the issues of both same-day and non-same-day stockpiling of supplies has been addressed. Non-same-day stockpiling is when a patient gets the next supply of a drug earlier than expected (ie. before the median time to re-supply). This most commonly occurs late in the calendar year when a patient is on the PBS

Safety Net. The risk of not allowing for this is that a break in treatment may be imputed for a patient early in the calendar year, where in fact the patient is simply consuming the stockpiled drug. The trade-off risk of allowing for non-same-day stockpiling is that a patient may consistently have a less than median time to re-supply (eg. because they have a high prescribed dose) and so the imputed coverage end date gets to be significant further than the real coverage end date. This means a break in treatment may be missed. In this KM analysis non-same-day stockpiling was not allowed for because the risk of stockpiling of these drugs was considered low.

Same-day stockpiling is deemed to have occurred when there are multiple supplies of the same PBS item on the same day. Supplies of different strengths on the same day is deemed to be necessary for the supply of the prescribed dose and so not considered to be stockpiling. Multiple supplies of the same strength on the same day are most likely due to stockpiling (ie. if such a quantity were required for the prescribed dose then the prescriber should have requested an increased maximum quantity). Thus same-day stockpiling is taken into account in this analysis.

## Appendix C: Listing history of PBS items for PAH medicines

Drug Name	Brand Name	Hospital Type	PBS Code	Form and Strength	Pack Size	Max Qty	Number of Repeats	DPMQ (Published)	Change Date			
BOSENTAN	Tracleer	Private	06429J	Tablet equivalent to 62.5 mg bosentan	60	60	0	\$4,035.00	1/03/2004			
					60	60	0	\$4,035.00	1/08/2007			
											\$4,081.42	1/07/2010
											\$4,081.52	1/07/2012
											\$4,081.63	1/07/2013
											\$2,923.10	1/08/2013
										\$2,923.23	1/07/2014	
						06430K	Tablet equivalent to 125 mg bosentan	60	60	0	\$4,035.00	1/03/2004
								60	60	0	\$4,035.00	1/08/2007
											\$4,081.42	1/07/2010
											\$4,081.52	1/07/2012
											\$4,081.63	1/07/2013
											\$2,923.10	1/08/2013
										\$2,923.23	1/07/2014	
		Public	05618Q	Tablet 62.5 mg (as monohydrate)	60	60	0	\$4,035.00	1/07/2010			
			05619R	Tablet 125 mg (as monohydrate)	60	60	0	\$4,035.00	1/07/2010			
								\$2,876.47	1/08/2013			
								\$2,876.47	1/08/2013			
ILOPROST	Ventavis	Private	06456T	Solution for inhalation equivalent to 20 micrograms iloprost in 2 mL ampoule	30	30	0	\$1,076.00	1/04/2005			
				Solution for inhalation 20 micrograms (as trometamol) in 2 mL	30	30	0	\$1,076.00	1/08/2007			
										\$1,122.42	1/07/2010	
										\$1,122.52	1/07/2012	
										\$1,122.63	1/07/2013	
										\$1,122.76	1/07/2014	
					Public	05751Q	Solution for inhalation 20 micrograms (as trometamol) in 2 mL	30	30	0	\$1,076.00	1/07/2010
						06477X	Powder for I.V. infusion equivalent to 500 micrograms epoprostenol with 1 vial diluent 50 mL	1	1	0	\$41.69	1/08/2006
							Powder for I.V. infusion 500 micrograms (as sodium) with 1 vial diluent 50 mL	1	1	0	\$41.69	1/08/2007
							Powder for I.V. infusion 500 micrograms (as sodium) with diluent	1	1	0	\$41.69	1/09/2008
								\$52.11	1/07/2010			
			06478Y	Powder for I.V. infusion equivalent to 1.5 mg epoprostenol with 2 vials diluent 50 mL	1	1	0	\$83.37	1/08/2006			

Drug Name	Brand Name	Hospital Type	PBS Code	Form and Strength	Pack Size	Max Qty	Number of Repeats	DPMQ (Published)	Change Date	
SILDENAFIL	Flolan Kit			Powder for I.V. infusion 1.5 mg (as sodium) with 2 vials diluent 50 mL	1	1	0	\$83.37	1/08/2007	
				Powder for I.V. infusion 1.5 mg (as sodium) with diluent	1	1	0	\$83.37	1/09/2008	
		Public	05731P	Powder for I.V. infusion 500 micrograms (as sodium) with diluent	1	1	0	\$93.79	1/07/2010	
			05732Q	Powder for I.V. infusion 1.5 mg (as sodium) with diluent	1	1	0	\$41.69	1/07/2010	
		Private	05036C	Powder for I.V. infusion, 500 micrograms (as sodium) infusion administration set	1	1	0	\$83.37	1/07/2010	
								\$52.11	1/01/2012	
								\$50.00	1/04/2012	
								\$50.10	1/07/2012	
								\$50.21	1/07/2013	
								\$50.34	1/07/2014	
				05042J	Powder for I.V. infusion, 1.5 mg (as sodium) infusion administration set	1	1	0	\$43.37	1/08/2014
								\$93.79	1/01/2012	
								\$89.65	1/04/2012	
								\$89.75	1/07/2012	
								\$89.86	1/07/2013	
								\$89.99	1/07/2014	
								\$77.31	1/08/2014	
		Public	05030R		Powder for I.V. infusion, 500 micrograms (as sodium) infusion administration set	1	1	0	\$41.69	1/01/2012
									\$39.62	1/04/2012
									\$33.28	1/08/2014
		Veletri	Private	05035B	Powder for I.V. infusion, 1.5 mg (as sodium) infusion administration set	1	1	0	\$83.37	1/01/2012
									\$79.23	1/04/2012
			10111E	Powder for I.V. infusion 500 micrograms (as sodium)	1	1	0	\$66.55	1/08/2014	
			10129D	Powder for I.V. infusion 1.5 mg (as sodium)	1	1	0	\$43.37	1/08/2014	
	Public		10117L	Powder for I.V. infusion 1.5 mg (as sodium)	1	1	0	\$77.31	1/08/2014	
			10130E	Powder for I.V. infusion 500 micrograms (as sodium)	1	1	0	\$66.55	1/08/2014	
			09605M	Tablet equivalent to 20 mg sildenafil	1	1	0	\$33.28	1/08/2014	
	Revatio	Private		Tablet 20 mg (as citrate)	90	90	0	\$898.43	1/03/2007	
					Tablet 20 mg (as citrate)	90	90	0	\$898.43	1/08/2007
								\$940.79	1/07/2010	
								\$940.89	1/07/2012	
								\$941.00	1/07/2013	
								\$941.13	1/07/2014	
	Public	09547L		Tablet 20 mg (as citrate)	90	90	0	\$791.63	1/08/2014	
								\$898.43	1/07/2010	

Drug Name	Brand Name	Hospital Type	PBS Code	Form and Strength	Pack Size	Max Qty	Number of Repeats	DPMQ (Published)	Change Date
	APO-Sildenafil PHT	Private	09605M	Tablet 20 mg (as citrate)	90	90	0	\$754.68 \$791.63	1/08/2014 1/08/2014
SITAXENTAN	Thelin	Public	09547L	Tablet 20 mg (as citrate)	90	90	0	\$754.68	1/08/2014
		Private	09622K	Tablet containing sitaxentan sodium 100 mg	30	30	0	\$2,743.80	1/04/2008
		Public	09551Q	Tablet containing sitaxentan sodium 100 mg	30	30	0	\$2,790.22	1/07/2010
AMBRISENTAN	Volibris			Both SITAXENTAN items delisted				\$2,743.80	1/07/2010
		Private	09648T	Tablet 5 mg	30	30	0	\$4,035.00	1/12/2009
								\$4,081.42	1/07/2010
								\$4,081.52	1/07/2012
								\$4,081.63	1/07/2013
								\$2,923.10	1/08/2013
								\$2,923.23	1/07/2014
			09649W	Tablet 10 mg	30	30	0	\$4,035.00	1/12/2009
								\$4,081.42	1/07/2010
								\$4,081.52	1/07/2012
								\$4,081.63	1/07/2013
								\$2,923.10	1/08/2013
								\$2,923.23	1/07/2014
		Public	05607D	Tablet 5 mg	30	30	0	\$4,035.00	1/07/2010
			05608E	Tablet 10 mg	30	30	0	\$2,876.47	1/08/2013
TADALAFIL	Adcirca	Private	01304P	Tablet 20 mg	56	56	0	\$4,035.00	1/07/2010
								\$2,876.47	1/08/2013
								\$878.49	1/04/2012
								\$878.59	1/07/2012
								\$878.70	1/07/2013
								\$878.83	1/07/2014
MACITENTAN	Opsumit	Public	01308W	Tablet 20 mg	56	56	0	\$838.53	1/04/2012
		Private	10134J	Tablet 10 mg	30	30	0	\$2,923.23	1/09/2014
		Public	10136L	Tablet 10 mg	30	30	0	\$2,876.47	1/09/2014

## **Disclaimer**

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