Public Funding of Bosentan for the Treatment of Pulmonary Artery Hypertension in Australia
Cost Effectiveness and Risk Sharing

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Abstract

Objectives: In Australia, no therapeutic agents were subsidised for the treatment of idiopathic pulmonary artery hypertension (iPAH), a rare progressive and severe disease with short life expectancy, until 1 March 2004, when bosentan (a dual endothelin receptor antagonist of high cost) was listed on the Pharmaceutical Benefits Scheme (PBS). Bosentan, in addition to conventional therapy, has been shown to slow iPAH progression and improve clinical and haemodynamic status and symptomatology, compared with placebo and conventional therapy. The objective of this paper is to describe the process of the Australian Pharmaceutical Benefits Scheme listing for bosentan (Tracleer®), which included a health economic model assessing the cost effectiveness of bosentan from a healthcare payer perspective, and a risk-sharing arrangement based on the establishment of a patient registry.

Methods: The health economic model predicted the cost, hospitalisation and mortality rates of a population of iPAH patients treated with either the conventional therapy regimen used in Australia or bosentan plus the conventional therapy regimen. The model was implemented as a first-order Monte Carlo simulation with mortality modelled directly as the main clinical outcome. The impacts of proposed continuation criteria, restricting the ongoing use of the drug, were evaluated. Costs and outcomes were discounted at 5% and a sensitivity analysis examined the robustness of the key assumptions.

Results: The model predicted that after 5, 10 and 15 years, the difference in average cumulative costs between bosentan plus conventional therapy and conventional therapy alone would be $A116,929, $A181,808 and $A216,331 for each patient, respectively. There would be an associated increase
in average life expectancy of 1.39, 2.93 and 3.87 years at 5, 10 and 15 years, respectively, with an incremental cost-effectiveness ratio at 15 years of A$55 927 for each life-year gained. Removing the continuation criteria from the model increased the incremental cost-effectiveness ratio to A$62 267 (1996–2002 values).

**Conclusions:** Economic modelling based on improved survival suggests bosentan to be a potentially cost-effective treatment for iPAH. However, the structure of the model and its inputs should be reviewed and updated as more data become available.

Pulmonary arterial hypertension (PAH) is a progressive disease of the lung vasculature characterised by increased pulmonary vascular resistance and a mean pulmonary arterial pressure of more than 25mm Hg at rest or 30mm Hg during exercise, with a normal pulmonary capillary wedge pressure.\[1\] PAH may be classified as idiopathic pulmonary artery hypertension (iPAH), formerly known as primary pulmonary hypertension (PPH), or alternatively, it may be present in association with other conditions such as connective tissue diseases (scleroderma or lupus), HIV or congenital heart defects. iPAH is rare, has an estimated incidence among the general population of one to two cases per million per year, a mean age of diagnosis of <50 years, and occurs more frequently in females.\[2\] The median life expectancy of patients with iPAH on conventional therapy alone is 2.8 years from diagnosis.\[3\] Prognosis is worse for patients with PAH associated with scleroderma, with a median survival on conventional therapy alone of <12 months.\[4\] The key determinant of survival is the degree of right ventricular function.\[5\]

The aims of PAH therapy are clinical improvement and prolongation of life. Existing treatments are limited by their effectiveness and safety (calcium channel antagonists), cost (epoprostenol and lung transplantation) and availability (lung transplantation).

Bosentan (Tracleer®)\[6\] is a dual endothelin receptor antagonist, and the first oral agent available in Australia for the treatment of PAH. Bosentan antagonises the activity of endothelin by blocking both of its target receptors, including those on the vascular endothelium and smooth muscle of the pulmonary vasculature, affecting the pathology which characterises iPAH, namely the hypertrophy, proliferation, *in situ* thrombosis and fibrosis of the pulmonary arteries and branch vessels.\[5\]

Consistent with the above, in two prospective, randomised, double-blind placebo-controlled clinical trials in patients with iPAH and PAH secondary to systemic sclerosis and lupus,\[2,6\] bosentan administration was associated with improved exercise capacity, cardiopulmonary haemodynamics, Borg dyspnoea index, WHO functional class, and time to clinical worsening at 12, 16 and/or 28 weeks.\[2,6\] In both trials, all patients continued to receive conventional therapy for PAH.

Specifically, Channick et al.\[6\] showed 43% of bosentan-treated patients improved from grade III to grade II in WHO functional class compared with 9% in the placebo group. There were also differences in cardiopulmonary haemodynamics (pulmonary vascular resistance, pulmonary artery pressure, pulmonary capillary wedge pressure, and mean right arterial pressure), with improvement in the bosentan group and deterioration in the placebo group. Results from the 6-minute walk test (6MWT) showed a 51m improvement on bosentan compared with 6m deterioration in the placebo group.

Rubin et al.\[2\] showed an increase of 46.5m for the 6MWT in patients treated with bosentan 250mg twice daily compared with a decrease of 8m in patients given placebo, and 39% of bosentan-treated patients improved WHO functional class compared

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1 The use of trade names is for product identification purposes only and does not imply endorsement.
Cost Effectiveness of Bosentan for PAH in Australia

with 30% of placebo patients. Open label extension from these trials provided observed survival data for up to 2.2 years, showing superior survival in iPAH patients treated with bosentan to that predicted for the same cohort of patients if they had been treated with conventional therapy only, as calculated from an equation generated from mortality data of historical controls enrolled in a National Institute of Health (NIH) registry of patients with iPAH.\(^3,7\)

Highland et al.\(^8\) modelled the cost effectiveness of bosentan at 1 year in comparison with two other PAH specific treatments (epoprostenol [Flolan\(^\circledR\)] and treprostinil [Remodulin\(^\circledR\)]) and found bosentan to be the most cost-effective alternative for the treatment of PAH in the US (from a societal perspective). However, in Australia, alternative pharmacological agents aimed specifically at PAH are not subsidised, and further, the availability of transplantation as a treatment option is severely limited. Alternative pharmacological treatment and transplant could not be used as direct comparators with bosentan under the Australian Pharmaceutical Benefits Advisory Committee (PBAC) guidelines.\(^9\) Hence, assessment of the cost effectiveness of bosentan therapy compared with the conventional therapy for PAH was required.

Bosentan was given ‘orphan drug’ status by the Therapeutic Goods Administration (TGA) in February 2001 for the treatment of iPAH and PAH associated with scleroderma, in patients with WHO functional class III or IV symptoms.\(^10\) Orphan drug status is assigned to treatments that are not normally commercially viable because of the cost of development of a pharmaceutical agent and the rarity of the disease. The Australian Orphan Drug Programme encourages sponsors to develop and market orphan drugs in Australia by waiving fees for marketing applications.\(^11\)

The TGA granted marketing approval for bosentan in November 2002. The PBAC recommendation for Pharmaceutical Benefits Scheme (PBS) listing of bosentan as a Section 100 Drug (Highly Specialised Drug), requiring private and public hospital authority, was given in December 2003. The PBAC did not invoke its ‘rule of rescue’ when considering bosentan, citing the availability of alternative interventions in Australia.\(^12\) 2

This paper presents a modelled evaluation of the long-term cost effectiveness of bosentan in the treatment of iPAH, based on a novel approach, including ongoing monitoring and risk-sharing. Under an agreement between the Australian Government and the sponsor pharmaceutical company, Actelion Pharmaceuticals Australia Pty Ltd (Actelion), the price of bosentan is directly linked to the observed survival of patients treated under the PBS.

Methods

Economic Model

The bosentan versus conventional therapy alone model is based on patients from the two aforementioned pivotal clinical trials of bosentan in patients with WHO functional class III or IV PAH,\(^2,6\) plus their long-term open-label extensions.\(^15\) These studies were the only placebo-controlled studies and focused on populations similar to those targeted for treatment in Australia. The model predicts the cost and outcomes of patients treated with bosentan therapy plus conventional therapy (‘Bosentan Therapy’) versus conventional therapy (‘Conventional Therapy’) alone, over a 15-year period. The impact of proposed continuation rules and other interventions, such as the addition of or switch to epoprostenol (intravenous epoprostenol) or lung transplant, are considered only in the sensitivity analysis.

2 A ‘rule of rescue’ is intended to reflect society’s expectation of a duty to save endangered life whenever possible and at whatever cost.\(^13,14\) Invoking a rule of rescue allows breakthrough high-cost pharmaceuticals for a low volume of patients to be considered for approval on the PBS under more lenient cost-effectiveness criteria. Some examples of the use of the rule of rescue have been imatinib mesylate (Glivec\(^\circledR\)) for patients in the chronic phase of chronic myeloid leukaemia, \(\beta\)-interferon for multiple sclerosis, and dornase alfa (Pulmozyme\(^\circledR\)) in cystic fibrosis patients. All require detailed authority and are listed as Section 100 (Highly Specialised Drugs) on the PBS.
The model, an individual patient level simulation, was implemented using the simulation software @Risk Version 4.5 (Palisade, Ithaca, NY, USA) in Microsoft® Excel. The Health States used in the model are shown in figure 1. The patient starts at either state I or state II, ‘on bosentan’ or ‘on conventional therapy’, respectively. At each step of the model, a random number is generated. The transition to the next health state occurs if the random number generated is less than or equal to the transition probability (presented in ‘Clinical assumptions’ below) for progression from the current health state to the subsequent health state (first-order Monte Carlo simulation). This set of random numbers was generated for each patient with or without bosentan treatment. At 6-month intervals, the patient was progressed through one or more health states. A total of 5000 iterations were performed.

Clinical Assumptions

**Conventional Therapy**

Conventional therapy is assumed to include diuretics, oral anticoagulants, calcium channel antagonists, supplemental oxygen therapy and/or inotropic agents.[16]

**Bosentan Treatment**

Bosentan dosage was calculated at an initial dosage of 62.5mg twice daily, titrated to 125mg twice daily, and was based on the dosages regimens used in the clinical trials in PAH. Bosentan was administered concomitantly with conventional therapy; 5% of patients were assumed to withdraw from treatment each year.

**Continuation Rule for Responders**

In an effort to evaluate the impact of proposed funding restrictions (i.e. the requirements requested by the PBAC and developed and implemented by the Health Insurance Commission, which is responsible for administering PBS listing requiring government authorisation), the original model was modified to explore the effect of a set of ‘continuation rules’ where the continuation of bosentan therapy was assumed only to occur in patients described as ‘responders’ to treatment with bosentan.[17] Clinically, responders are defined as those patients who show stabilisation or improvement, based on two out of three of the following outcome parameters: (i) composite assessments from right heart catheterisation; (ii) echocardiography; or (iii) the 6MWT.[17,18] Outcome parameters are reassessed 6-monthly.

There are no data on which to base a model of the impact of discontinuation criteria such as those imposed by the Health Insurance Commission. The intention of the criteria is to identify patients who will no longer benefit from bosentan, and hence reduce costs with minimal impact on effectiveness. These criteria were implemented retrospectively into the model by making three changes:

1. An additional 20% of patients would be withdrawn from bosentan after 6 months of treatment. Withdrawal rates were based on the withdrawal
rates due to ‘lack of benefit’, in the Australian multicentre bosentan study.[19]
2. Mortality rates while on bosentan were reduced to reflect the fact that patients who continued on drug were selected by the continuation rules (figure 2).
3. It was assumed that by identifying patients in decline, the continuation rules would lead to early withdrawal of drug in patients no longer benefiting from bosentan, and hence bosentan costs would be reduced to zero in those patients for a defined period before death (figure 3).

Hospitalisation
Hospitalisation rates were extrapolated from the results of a retrospective analysis of the first 16 weeks of a bosentan clinical trial [2] (table I).

Mortality
The mortality rate in patients receiving conventional therapy alone was set at 26.6% per annum. This was estimated by using the baseline measurement of right ventricular function (specifically, mean pulmonary arterial pressure, mean right atrial pressure, and cardiac index) from the patients entering the bosentan clinical trial’s long-term follow-up (including patients from both clinical trials and hence pre-bosentan baseline characteristics), and entering those data into the prediction equation developed by the NIH in the US (validated by Sandoval et al.[21] and calculated using a proportional hazards survival model[3]). The mortality rate of bosentan-treated patients (5.2% per annum) was based on the long-term follow-up (up to 2.2 years) of patients entering the two bosentan randomised clinical trials.[2,6] Due to the small number of deaths, the mortality rate was calculated based on the full period of available data using the person-year method.

In modelling the selective continuation of responders, it was assumed that ‘responders’ would have a lower mortality rate than a mix of ‘responders’ and ‘non-responders’ who continued treatment with bosentan, as was the case in the clinical trials. The mortality for patients who responded on bosentan was thus adjusted to give the same overall life-years gained as the model with no continuation rule, and consequently the mortality rate for ‘responders’ to bosentan was set at 2.8% per year. This was calculated by running the model with various ‘responder’ mortality rates until the total life-year gained was the same as that with no selection of ‘responders’ or no continuation rule.

Epoprostenol (Sensitivity Analysis Only)
Use of epoprostenol is rare in Australia and hence the rate of intervention with epoprostenol was set at zero in the base-case model. Epoprostenol treatment was only considered in the sensitivity analysis and use in 0.5%, 1.5% and 2.5% of patients per year (expert opinion of AK, KM, RW and TW [authors]) was assessed. Patients receiving conventional therapy alone, including those who were withdrawn from bosentan treatment, were eligible for epoprostenol. Mortality rates of those treated with epoprostenol were assumed to be the same as mortality rates of those treated with bosentan.[22,23]

![Fig. 3. The ‘Continuation Rule’ as applied to the bosentan vs conventional therapy alone model. Disease progression and responder states are defined in terms of exercise capacity as measured by the 6-minute walk test (6MWT), and composite assessments from echocardiography and/or by right heart catheterisation. Bosentan assumed to have been withdrawn 12 months prior to death based on non-response. PAH = pulmonary arterial hypertension; † = 6-month reviews.](image-url)
Lung Transplantation (Sensitivity Analysis Only)

Heart-lung or lung transplantation were only considered in the sensitivity analysis and were assumed to be performed in 2%, 4% and 6% of patients per year.\cite{24} Transplantation as treatment for PAH is limited and is dependent on organ availability. If patients were withdrawn from bosentan treatment, they had a chance of receiving transplantation. Operative mortality of patients undergoing transplantation was assumed to be 19% and subsequent mortality rates to be 3.4% per 6-month cycle.\cite{25}

Cost Estimates from the Australian Healthcare Perspective

Bosentan

The public cost of bosentan was 107.60 Australian dollars ($A) for each patient per day, or $A39 300 per patient per annum (2004 PBS costing).\cite{18} This cost was based on a rebate programme agreed between the Australian Government and Actelion. Costs of conventional therapy were added to the costs of bosentan, and epoprostenol.

Conventional Therapy

Conventional therapy was defined after discussion with key clinicians and is outlined in Keogh and Wlodarczyk.\cite{26} Conventional therapy was valued at $A249 per 6 months (2002 values), and included: warfarin, recommended wherever not contraindicated; calcium channel antagonists, especially in patients who were ‘pressure’ responders; and supplementary therapy, which may include oxygen, diuretics, spironolactone and angiotensin-converting enzyme inhibitors. Medical costs including 6MWT, lung function testing, blood tests, chest x-rays, echocardiograph, electrocardiograph and specialist fees were valued at $A567 per 6 months (see table II for further details; 2001 values). Conventional therapy costs were the same for both treatment arms and did not differ with severity.

Hospitalisation

The cost of hospitalisation was estimated using Australian Refined Diagnosis Related Groups (AR-DRG version 4.1)\cite{29} descriptions F62A (Heart Failure and Shock plus catastrophic complications) and F62B (Heart Failure and Shock minus catastrophic complications), to give a weighted cost of $A564.66 per day. For simplicity, the cost of hospitalisation was estimated at $A500 per day (2001/2 values).

Epoprostenol

The cost of epoprostenol was $A250 for each 1.5mg ampoule, including two vials of diluent. For the initial 6 months, the dose of epoprostenol was

<table>
<thead>
<tr>
<th>Table II. Components of conventional therapy\cite{27,28}a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>Exercise test\textsuperscript{b}</td>
</tr>
<tr>
<td>Lung function</td>
</tr>
<tr>
<td>Chest x-ray</td>
</tr>
<tr>
<td>Echocardiogram</td>
</tr>
<tr>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>Blood tests</td>
</tr>
<tr>
<td>Specialist</td>
</tr>
<tr>
<td><strong>Total medical</strong></td>
</tr>
<tr>
<td>Frusemide (furosemide) 40mg</td>
</tr>
<tr>
<td>Spironolactone 100mg</td>
</tr>
<tr>
<td>Warfarin 5mg</td>
</tr>
<tr>
<td>Diltiazem 60mg</td>
</tr>
<tr>
<td><strong>Total pharmaceutical</strong></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Cost reported in Australian dollars ($A) [2001/2 values].
\textsuperscript{b} The cost of a supervised exercise test is used in lieu of no MBS listing for a 6-minute walk test.
\textsuperscript{c} Cost per month.

MBS = Medicare Benefits Schedule, November 2001; PBS = Pharmaceutical Benefits Scheme, August 2002; tabs = tablets.
estimated to be 9 ng/kg/min, increasing by 8 ng/kg/min in each subsequent 6-month period of the model to a maximum of 97 ng/kg/min. By 1 year, the average dose of an adult patient would therefore be 17 ng/kg/min (the equivalent of one ampoule per day), at an annual cost of $A91 250 or a daily cost of $A250 based on 2002 costings. Drug delivery costs, which included delivery equipment, consumables and hospitalisation, were estimated at $A10 795 for the first 6 months and $A6209 for subsequent 6 months (2001/2 values).[31]

**Lung Transplantation**

The cost of lung transplant was adapted from the superspecialty service guidelines for lung transplant services.[24] The total first year cost of lung transplant was $A192 500, which was broken down into pre-transplant and transplant costs of $A96 900 and post-transplant costs of $A95 600. All transplant costing data were based on the 1996–7 financial year and was not updated to 2002 levels, as neither the consumer price index in Australia nor non-volatile items averaged >0.5% per annum increase over the period 1997–2002.

Transplant costs included referral and assessment ($A5200), pre-transplant costs ($A11 400), organ retrieval ($A15 200) and transplantation ($A65 100), which included all other associated costs. Most of these costs were applied in the first 6 months, with only $A3500 in anti-rejection drugs being applied in the second 6-month period after transplant.

Post-transplant costs included hospitalisation, drugs (except anti-rejection drugs), pathology, radiation, transport and accommodation. In the first 6 months, post-transplant costs were $A73 252. In the second 6-month period, post-transplant costs were $A22 348.

After year 1, costs per 6-month period were $A25 848, comprising $A3500 for anti-rejection drugs, given on an outpatient basis, and $A22 348 for post-transplant adverse events.

**Discounting**

In accordance with the Australian Guidelines, all costs and life-years gained were discounted at a rate of 5% per year.

**Sensitivity Analysis**

There were insufficient data available to support a probabilistic sensitivity analysis, so a series of one-way sensitivity analyses were run around the base-case continuation rule model. Of particular importance was the impact of changes in the mortality rate. This was assessed by halving and doubling the relative risk of bosentan versus usual care and the absolute mortality rate in the usual care group. In addition, the duration of benefit was reduced to 5 years by setting relative risk to one for years 6–15. A similar approach of halving and doubling base-case assumptions was used for all other inputs except interventions with epoprostenol and transplantation, which were based on a range of plausible rates elicited from clinicians with recent experience in these areas.

**Results**

At 1, 5 and 15 years, survival rates of bosentan-treated patients were estimated at 92.6%, 67.4% and 29.3%, respectively, compared with a predicted survival of 73.7%, 21.7% and 0.7% for the same patients receiving conventional therapy alone. For bosentan-treated patients, there would be an associated increase in average life expectancy of 1.39, 2.93 and 3.87 years at 5, 10 and 15 years, respectively. Figure 4 shows the percentage of patients predicted to be alive for bosentan and conventional therapy alone over the 15-year period.

Patients treated with conventional therapy alone had a discounted mean life expectancy of 2.8 years, compared with 6.7 years in patients treated with bosentan.

The discounted mean cost in the bosentan group over the 15-year modelled period was $A234 618 compared with $A18 287 for conventional therapy alone. In the bosentan group this comprised $A210 966 for pharmaceuticals, $A16 064 for hospitalisation and $A7588 for medical costs compared with $A1406, $A13 679 and $A3202, respectively, for conventional therapy alone. The model predicted that after 5, 10 and 15 years, the difference in average cumulative costs between bosentan plus conventional therapy and conventional therapy
alone would be $A116,929, $A181,808 and $A216,331 for each patient, respectively. The incremental cost-effectiveness ratio (ICER) of treatment reduced over time from $A84,231 per year of life saved at 5 years to $A55,927 per year of life saved at the end of the 15-year period. Removing the continuation criteria from the model increased the incremental cost-effectiveness ratio to $A62,267.

Sensitivity Analysis

The sensitivity analysis examined the impact of key assumptions on the ICER. Assumptions about mortality rates were key determinants of changes in cost effectiveness of bosentan treatment. Halving of the annual mortality rate in patients treated with conventional therapy from 26.6% to 13.9% resulted in an increase in the incremental cost per life-year from $A55,927 to $A73,229.

Removing the PBS continuation rules from the model increased the ICER to $A62,267 from $A55,927.

The ICER was also sensitive to assumptions about epoprostenol treatment or lung transplantation, with even modest rates of intervention of 0.5% per year of epoprostenol use, in randomly selected non-bosentan treated patients, reducing the ICER to $A42,260, and heart-lung transplantation rates of 2% resulting in an ICER of $A54,133.

The cost of conventional therapy, number or risk of hospitalisations did not greatly affect the ICER. Table III provides an overview of the sensitivity analyses.

Discussion

The key assumption of this model was that bosentan increases life expectancy of patients diagnosed with iPAH. While this assumption is not based directly on randomised clinical trial evidence, it is based on strong epidemiological and clinical trial data showing clear improvements in intermediate outcomes and low mortality rates during long-term open label follow-up of the main studies for bosentan in PAH. McLaughlin et al. have recently published an analysis of the bosentan long-term follow-up data, to 3.3 years, and updated comparisons with the NIH registry-predicted survival, including discussion of the potential for bias in estimating mortality rates because of the use of interventions such as epoprostenol in some patients.

To account for the relatively young age of the patients diagnosed with iPAH, the economic model was extended for a 15-year period, and predicted that 29.3% of bosentan-treated patients would still be alive at this time point. The ICER is reduced from $84,231 per life-year saved at 5 years to $55,927 per life-year saved at 15 years. Modelling over a shorter duration, for example 2 years, would assume that there is no benefit beyond 2 years, an implicit assumption which could underestimate the benefit of bosentan. Nevertheless, the relatively short period for which mortality data are available is a major limitation in evaluating the cost effectiveness of bosentan.
Table III. Sensitivity analysis on the model; discounted results at 15 years<sup>a</sup>

<table>
<thead>
<tr>
<th>Sensitivity description</th>
<th>Base value</th>
<th>Sensitivity value</th>
<th>Total average cumulated cost</th>
<th>Life-years gained</th>
<th>Incremental cost per life-year gained</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>bosentan cohort</td>
<td>conventional therapy alone cohort</td>
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<tr>
<td><strong>Base-case continuation rule</strong></td>
<td></td>
<td></td>
<td>234 618</td>
<td>3 868</td>
<td>55 927</td>
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<tr>
<td>Remove continuation rule</td>
<td>Yes</td>
<td>No</td>
<td>258 214</td>
<td>18 287</td>
<td>3.853</td>
</tr>
<tr>
<td>Conventional therapy mortality (per year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>decrease conventional therapy mortality (approximately halved)</td>
<td>26.6%</td>
<td>13.9%</td>
<td>264 930</td>
<td>32 001</td>
<td>3.181</td>
</tr>
<tr>
<td>increase conventional therapy mortality (by approximately 50%)</td>
<td>26.6%</td>
<td>38.2%</td>
<td>210 677</td>
<td>12 333</td>
<td>3.938</td>
</tr>
<tr>
<td>Mortality RR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>increase RR of bosentan mortality (all years doubled)</td>
<td>0.1</td>
<td>0.20</td>
<td>199 517</td>
<td>18 287</td>
<td>3.063</td>
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<tr>
<td>decrease RR of conventional therapy mortality (all years halved)</td>
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<td>0.05</td>
<td>258 287</td>
<td>18 287</td>
<td>4.395</td>
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<tr>
<td>increase RR of conventional therapy mortality (years 6–15)</td>
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<td>1.0</td>
<td>166 253</td>
<td>18 287</td>
<td>2.373</td>
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<td>Mortality and hospitalisation RR (2-way, years 6–15)</td>
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<tr>
<td>mortality</td>
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<td>18 287</td>
<td>2.373</td>
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<tr>
<td>hospitalisation</td>
<td>0.62</td>
<td>1.0</td>
<td>167 694</td>
<td>18 287</td>
<td>2.373</td>
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<tr>
<td>Conventional therapy cost (per 6 months)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>increase cost of conventional therapy (doubled)</td>
<td>816</td>
<td>1632</td>
<td>245 539</td>
<td>22 895</td>
<td>3.868</td>
</tr>
<tr>
<td>decrease cost of conventional therapy (halved)</td>
<td>816</td>
<td>408</td>
<td>229 158</td>
<td>15 983</td>
<td>3.868</td>
</tr>
<tr>
<td>Conventional therapy hospitalisations (per year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>increase conventional therapy hospitalisations (doubled)</td>
<td>0.75</td>
<td>1.5</td>
<td>250 771</td>
<td>32 161</td>
<td>3.868</td>
</tr>
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<td>decrease conventional therapy hospitalisations (halved)</td>
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<td>0.375</td>
<td>226 568</td>
<td>11 639</td>
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<tr>
<td>Hospitalisation cost (per day)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>increase cost of hospitalisation (doubled)</td>
<td>500</td>
<td>1000</td>
<td>250 682</td>
<td>31 966</td>
<td>3.868</td>
</tr>
<tr>
<td>decrease cost of hospitalisation (halved)</td>
<td>500</td>
<td>250</td>
<td>226 586</td>
<td>11 448</td>
<td>3.868</td>
</tr>
<tr>
<td>Withdrawals from bosentan (per year)</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>decrease withdrawals from bosentan</td>
<td>5%</td>
<td>0%</td>
<td>303 432</td>
<td>18 287</td>
<td>4.931</td>
</tr>
<tr>
<td>decrease withdrawals from conventional therapy (doubled)</td>
<td>5%</td>
<td>2.5%</td>
<td>266 469</td>
<td>18 287</td>
<td>4.375</td>
</tr>
<tr>
<td>increase withdrawals from bosentan</td>
<td>5%</td>
<td>10%</td>
<td>191 855</td>
<td>18 287</td>
<td>3.180</td>
</tr>
<tr>
<td>Discontinuation rule (months prior to death)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>discontinued bosentan 6 months prior to death (later)</td>
<td>12mo</td>
<td>6mo</td>
<td>238 782</td>
<td>18 287</td>
<td>3.868</td>
</tr>
<tr>
<td>discontinued bosentan 18 months prior to death (earlier)</td>
<td>12mo</td>
<td>18mo</td>
<td>230 094</td>
<td>18 287</td>
<td>3.868</td>
</tr>
</tbody>
</table>

<sup>a</sup>Continued next page
As well as drug acquisition costs, the average costs of the bosentan cohort included the continuing treatment costs associated with living longer versus those undergoing conventional therapy alone. The longer patients live, the more cost will be involved in maintaining therapy and any subsequent hospitalisation. Hence, there is a direct link between improved survival and costs in bosentan-treated patients.

Like most economic appraisals this model assumes that treatment options and costs remain unchanged well beyond the observed trial data. That is, the model does not allow for developments in the pharmaceutical and health industries over time. Hence, the structure of the model and its inputs should be reviewed and updated as new options appear.

The modelling framework has a number of other limitations. Most importantly, the model is based on limited clinical data and for this reason we did not proceed to a probabilistic assessment of uncertainty (second-order Monte Carlo simulation). Exploring the impact of a clinically complex continuation rule required simplifying assumptions which can only be assessed retrospectively.

Adverse events have not been explicitly involved in the model because occurrences are rare\(^2\) and able to be managed with dose adjustments, hence not requiring additional resources. Similarly, the costs of monitoring for adverse events would be minor in comparison to costs of treatment.

Overall, this model suggests that bosentan therapy is significantly more costly than conventional therapy for patients with iPAH. However, the increased cost is associated with an estimated average increase in life expectancy of 3.8 years.

The economic model supporting bosentan is based on iPAH patients only. Idiopathic PAH patients represent approximately two-thirds of PAH patients in the clinical trials, and hence two-thirds of patients qualifying for bosentan. Bosentan is also indicated for use in PAH related to scleroderma in both adults and children. Data in these aetiological subgroups is relatively limited; however, mortality rates are likely to be higher relative to iPAH, with
recent estimates suggesting a mortality rate of 50% in the first year.\[^{34,35}\]

Defining Responders and Continuation

The imposition of the continuation rule on the ongoing prescribing of bosentan is intended to restrict PBS-subsidised treatment to only those patients who benefit from the drug, which is apparent by stabilisation or improvement of clinically relevant endpoints. This reflects the concern that in the absence of appropriate alternatives an expensive drug would continue to be used in patients who decline despite treatment. Similar restrictions have been imposed on PBS availability of drugs for dementia and rheumatoid arthritis.\[^{36}\] The restriction will reduce the total cost to the government for the funding of bosentan and hence improve cost effectiveness if there is no loss of benefit resulting from the restriction: that is, the restriction must accurately identify patients as non-responders. Where there is misclassification of responders, such that patients who would have benefited from treatment are no longer subsidised, total costs will still be reduced but the impact on cost effectiveness is less clear.

The existence of clinically objective criteria for assessing response, which includes stabilisation, might also encourage some doctors and patients to continue treatment where they might otherwise discontinue treatment based on subjective assessments.

Discontinuation of the PBS subsidy for bosentan in non-responders, based on strict continuation criteria,\[^{17}\] creates an obvious medical/ethical dilemma due to the inherently progressive and rapid nature of iPAH, leaving the patient with no potentially effective therapeutic alternative. The clinical impact of the continuation rules remains to be assessed over time with experience in the Australian population supplied with PBS listed bosentan.

Bosentan Patient Register – Risk-Sharing Strategy

Cost-effectiveness ratios of <$A60 000 for each life-year saved are generally considered acceptable in Australia.\[^{37}\] However, the cost-effectiveness model presented to the PBAC was based on the assumption of a substantial increase in life expectancy in bosentan-treated patients. The assumption has not been confirmed in a randomised placebo-controlled trial for practical and ethical reasons. Hence, a unique 3-year risk-sharing agreement was established between the Australian Government and Actelion, whereby the price of bosentan is directly linked to the observed survival of iPAH patients treated with bosentan under the PBS subsidy. The price of bosentan will be altered if the observed survival in PBS-treated patients differs from that predicted by the economic model. Price reductions will be aimed at maintaining the incremental cost-effectiveness ratio for iPAH patients at no worse than that predicted in the model.

Price reductions will be triggered once the lower (least favourable) 95% confidence limit for the observed mortality in patients treated with PBS-subsidised bosentan exceeds that of the predicted mortality rate of 5.2% per annum. The precision with which mortality rates are estimated will depend on the number of patients, the length of follow-up, and the survival estimates. Assuming 150 patient-years – e.g. 150 patients, 1 year follow-up and a 5% annual mortality rate – the 95% confidence interval will be ±3.5% (95% CI 1.5, 8.5). As the number of patients and the duration of follow-up increases, the standard error and hence the confidence interval for mortality will decrease. For example, after 300 patient-years of experience, the confidence interval will decrease to approx ±2.5%. In this situation, price reductions will be triggered where the observed annual mortality is 8.7% or more.

To facilitate accurate monitoring of bosentan-treated patients, an independently managed ‘Bosentan Patient Register’ (BPR) was established. The register will collect information regarding survival and treatment of iPAH in Australia, thereby facilitating a better understanding of the management of iPAH. Further, it will ensure that the PBAC can periodically review the survival rates of bosentan-treated iPAH patients, compared with the survival rates predicted in the modelling process.

Risk sharing strategies provide a mechanism through which decision makers can consider explicit

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areas of uncertainty surrounding the cost effectiveness of a drug and incorporate these into funding agreements. Where the major concern is over the total budgetary impact of a new drug, risk-sharing strategies might take the form of a price-volume agreement. In cases where uncertainty is related to long-term clinical outcomes, risk-sharing based on outcomes provides alternatives to continued delays in decision making.

Sudlow and Counsell\textsuperscript{[38]} are critical of a number of factors which form the basis of risk-sharing strategies. Concern is based largely on potential operational difficulties and a lack of scientific rigor. The number of treatments for which such a strategy can be scientifically justified is limited, and careful evaluation of the biases associated with decision making based on uncontrolled studies is critical. These factors need to be balanced against the potential benefits of earlier access to treatment.

**Conclusion**

Economic modelling based on improved survival shows bosentan to be a potentially cost-effective treatment for iPAH. However, due to practical and ethical constraints, the survival benefits cannot be confirmed in a randomised placebo-controlled trial. Ultimately, the PBS listing of bosentan was facilitated by the establishment of expert centres, the development of clinical guidelines to monitor patient progress, and a risk-sharing strategy whereby the price of bosentan is directly related to survival observed prospectively in a patient registry. In situations where long-term placebo-controlled trials are unlikely to become available, this strategy allows timely access to important new treatments.

**Acknowledgements**

All submissions to the PBAC were funded by Actelion Pharmaceuticals Australia. The Manuscript was compiled with financial support from Actelion Pharmaceuticals Australia.

John Wlodarczyk is a consultant to Actelion Pharmaceuticals Australia. Les Cleland has acted as a consultant to Actelion Pharmaceuticals Australia and the Pharmaceutical Benefits Scheme (PBS). Anne Keogh has participated in clinical trials with Actelion Pharmaceuticals Australia, Myogen, Encysive, Pfizer, Roche, Novartis and Ventracor. She has acted as a consultant to Actelion Pharmaceuticals Australia, Pfizer, Roche, Wyeth and Novartis. Keith McNeil has served on advisory boards for Actelion Pharmaceuticals Australia and GSK. Kate Perl acted as a consultant to Actelion Pharmaceuticals Australia. Trevor J. Williams is an investigator for Actelion Pharmaceuticals Australia, Pfizer, Novartis and GSK funded studies. He is also on the Advisory Board for Actelion Pharmaceuticals Australia and GSK. Andrew Mitchell, Director, Pharmaceutical Evaluation Section, Australian Department of Health and Ageing and David Kwasha, Managing Director of Actelion Pharmaceuticals Australia reviewed and commented on an earlier draft of this paper.

All authors were part of an advisory board convened by Actelion Pharmaceuticals Australia, which contributed to the development of the model and risk sharing arrangement.

The manuscript and the economic model were prepared by John Wlodarczyk, Anne Keogh, Les Cleland, Keith McNeil, Kate Perl, Robert Weintraub and Trevor Williams reviewed drafts of the paper.

**References**


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