Objectives: Bosentan, a dual endothelin receptor antagonist (ERA), was the first oral drug approved for the treatment of pulmonary arterial hypertension (PAH), a rare disease with poor prognosis. In 2004 the Australian Department of Health agreed to fund bosentan on the pharmaceutical benefits scheme (PBS) on the condition that a registry was established to monitor mortality: if the observed mortality rate was higher than that claimed in the original funding submission then the price of bosentan would be reduced to maintain the original incremental cost-effectiveness ratio (ICER). This article presents the economic implications of the bosentan patient registry (BPR).

Methods: An existing economic model was updated using the results of the BPR. Participation rates were high and the BPR collected 821 patient years of follow-up on 528 patients. Based on the observed raw mortality a 23.7% price reduction would have been needed to maintain the original ICER in idiopathic PAH patients. After allowing for the higher risk patients actually treated in Australia, a 13.5% reduction in bosentan price would have been required. In 2008, however, sitaxentan, a new oral ERA PAH treatment was listed on the PBS at a 15% discount to bosentan. On the basis of cost-minimization, bosentan was forced to reduce its price to that of sitaxentan. After this price reduction the ICER for bosentan was similar to that originally proposed and hence, no additional price reduction was sought by the Pharmaceutical Benefits Advisory Committee (PBAC).

Conclusions: The bosentan PAH registry provided a useful mechanism for monitoring the cost-effectiveness of bosentan after funding approval.

Keywords: bosentan, pharmaceutical funding, risk-share agreement.

Introduction

Risk-sharing agreements in which price is linked to ongoing data collection have been widely discussed but few practical case studies are available [1–8]. Bosentan, a dual endothelin receptor antagonist (ERA) was the first oral drug approved for the treatment of pulmonary arterial hypertension (PAH), a rare disease with poor prognosis. In 2004 the Australian Department of Health agreed to fund bosentan on the pharmaceutical benefits scheme (PBS) on the condition that a registry was established to monitor mortality. The future price of bosentan would be adjusted based on the results of the registry [9]. If the observed mortality rate was higher than that claimed in the original funding submission then the price of bosentan would be reduced to maintain the original incremental cost-effectiveness ratio (ICER). This article presents the economic implications of the bosentan patient registry (BPR). The original ICER in idiopathic PAH patients. After allowing for the higher risk patients actually treated in Australia, a 13.5% reduction in bosentan price would have been required. In 2008, however, sitaxentan, a new oral ERA PAH treatment was listed on the PBS at a 15% discount to bosentan. On the basis of cost-minimization, bosentan was forced to reduce its price to that of sitaxentan. After this price reduction the ICER for bosentan was similar to that originally proposed and hence, no additional price reduction was sought by the Pharmaceutical Benefits Advisory Committee (PBAC).

Results of the registry

The registry had excellent response from clinicians and patients with 821 patient years of follow-up on 528 patients and a participation rate of 90%.

Results and discussion

The registry had excellent response from clinicians and patients with 821 patient years of follow-up on 528 patients and a participation rate of 90%. Participation rates were high and the BPR collected 821 patient years of follow-up on 528 patients. Based on the observed raw mortality a 23.7% price reduction would have been needed to maintain the original ICER in idiopathic PAH patients. After allowing for the higher risk patients actually treated in Australia, a 13.5% reduction in bosentan price would have been required. In 2008, however, sitaxentan, a new oral ERA PAH treatment was listed on the PBS at a 15% discount to bosentan. On the basis of cost-minimization, bosentan was forced to reduce its price to that of sitaxentan. After this price reduction the ICER for bosentan was similar to that originally proposed and hence, no additional price reduction was sought by the Pharmaceutical Benefits Advisory Committee (PBAC).
The mortality rate in idiopathic PAH (iPAH) was 11.8% per annum (95% CI, 8.8–14.8) compared with the 5.2% predicted by the economic model. The patients enrolled in the registry, however, were older and had more severe disease than those in the clinical trials on which the agreement was based. The registry data clearly revealed that older patients with more severe disease (World Health Organization Functional Class IV [WHO FC IV]) had higher mortality rates [13].

The age and severity-specific mortality rates for the registry were used to calculate an adjusted mortality rate. This was done by calculating age and severity-specific mortality rates from the BPR and then lowering the percent of older and more severe patients to that seen in the randomized controlled trials (RCTs). This adjusted estimate of mortality was 8.8%.

Originally the focus of the economic model and the registry agreement were on iPAH patients. However, associated PAH (systemic sclerosis) patients, or APAH-SSc, formed a larger proportion of the treatment population than expected: 42% of registry patients were of APAH-SSc etiology compared with 21% of the RCT populations. Associated PAH-SSc patients were generally thought to have a worse prognosis than iPAH patients with annual mortality rates in the order of 45% [14–16]. The observed APAH-SSc mortality rate from the BPR was 16.6%.

### Pricing implications

Using the same assumptions as the original model [9], the observed raw mortality rate of 11.8% per annum would have resulted in an ICER of AUD$80,735 per life year gained and a 23.7% price reduction would have been necessary to maintain the original ICER of AUD$62,267. After weighting to the trial population (mortality rate of 8.8%), the ICER was reduced to AUD$69,811 and a 13.5% reduction in bosentan price would have been required. Including APAH-SSc patients in the model would have further improved the ICER to AUD$64,427 per life year gained (Table 1).

Bosentan was followed by a number of competitors in the market (epoprostenol sodium [Flolan, GlaxoSmithKline, Research Triangle Park, NC], iloprost, sitaxentan, ambrisentan, sildenafil [Revatio, Pfizer Inc, New York, NY]). In a process independent of the registry, sitaxentan, another oral ERA was listed on the PBS in 2008 at a 15% price discount to bosentan (for patients with iPAH/APA-SSc, and FC III). The PBAC then requested a price decrease for bosentan to match the discount to bosentan (for patients with iPAH/APAH-SSc, and FC III).

The BPR provided data on patients with iPAH and APAH-SSc, their treatment, and their survival which supported continued public funding of bosentan. Risk-sharing arrangements that rely on monitoring objective measurable outcomes can play a valuable role in establishing cost-effectiveness.

### Acknowledgments

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John Wlodarczyk has worked as a consultant for Actelion Pharmaceuticals. Christopher M Reid is employed by Monash University; the university was contracted to manage the BPR. He does not have a financial arrangement with Actelion Pharmaceuticals.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Annual mortality rate</th>
<th>Total cost</th>
<th>Years of life</th>
<th>ICER cost/YOL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>iPAH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observed mortality</td>
<td>11.8%</td>
<td>25%</td>
<td>$160,939</td>
<td>$18,332</td>
</tr>
<tr>
<td>Adjusted mortality*</td>
<td>8.8%</td>
<td>25%</td>
<td>$185,121</td>
<td>$18,332</td>
</tr>
<tr>
<td><strong>SSc</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Versus Kawut et al. [15]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observed</td>
<td>16.6%</td>
<td>45%</td>
<td>$127,904</td>
<td>$9165</td>
</tr>
<tr>
<td>Adjusted</td>
<td>14.12%</td>
<td>45%</td>
<td>$141,763</td>
<td>$9165</td>
</tr>
<tr>
<td>Weighted iPAH (58%) and SSc (42%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observed</td>
<td>13.6%</td>
<td>34.3%</td>
<td>$146,729</td>
<td>$13,585</td>
</tr>
<tr>
<td>Adjusted</td>
<td>11.3%</td>
<td>34.3%</td>
<td>$165,679</td>
<td>$13,773</td>
</tr>
</tbody>
</table>

ICER, incremental cost-effectiveness ratio; iPAH, idiopathic pulmonary arterial hypertension; SSc, systemic sclerosis; YOL, year of life.

* Adjusting age and severity to that of the key clinical trials.
REFERENCES


ERRATUM

The article "Economic Evaluation of Reamed versus Unreamed Intramedullary Nailing in Patients with Closed and Open Tibial Fractures: Results from the Study to Prospectively Evaluate Reamed Intramedullary Nails in Patients with Tibial Fractures (SPRINT)," by Briel et al. was published in Value in Health 2011;14:450–7. The correct author by-line is as follows: The SPRINT Investigators. The full listing of the SPRINT Investigators who took part in the collaboration of this article can be found in the Acknowledgments section of the article.

ERRATUM

The article "Economic Impact of Nonpersistence with Antidepressant Treatment in the Adult Population of Quebec: A Comparative Cost-Effectiveness Approach," by Béland et al (Value in Health 2011;14:492-8), was published with an incorrect Figure 1. The correct Figure 1 is shown below.

Fig. 1 – Mean total costs and effectiveness of alternative antidepressant treatment.