

**6.8 BOSENTAN, 62.5 mg tablet, 60; 125 mg tablet, 60; Tracleer®  
EOPROSTENOL, 500 microgram injection vial, 1; 1.5 mg  
injection vial, 1; Veletri®  
MACITENTAN, 10 mg tablet, 30; Opsumit®  
Actelion Pharmaceuticals Australia Pty Ltd**

**1 Purpose of Application**

- 1.1 The minor submission requested amending the current 'continuing treatment' restriction of pulmonary arterial hypertension (PAH) agents to remove the requirement that:
- (i) the patient must have been assessed as having achieved a response to their most recent course of treatment; and
  - (ii) clinicians must provide evidence that a patient has been assessed as having achieved response when wanting to prescribe continued treatment.

**2 Requested listing**

- 2.1 The submission sought the following changes to the existing 'continuing' restriction for current listings of PAH agents (the restriction below does not include administrative advice or cautions, which differ between the individual PAH agents and are not affected by the proposed changes):

Name, Restriction, Manner of administration and form	Max. Qty packs	Nº.of Rpts	Proprietary Name and Manufacturer	
BOSENTAN bosentan 62.5 mg tablet, 60 bosentan 125 mg tablet, 60	1 1	0 0	Tracleer	Actelion Pharmaceuticals
EOPROSTENOL epoprostenol 500 microgram injection, 1 x 500 microgram vial epoprostenol 1.5 mg injection, 1 x 1.5 mg vial	1 1	0 0	Veletri	
MACITENTAN macitentan 10mg tablet, 30	1	0	Opsumit	

<b>Category / Program</b>	Section 100 – Highly Specialised Drugs Program
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	-
<b>Severity:</b>	-
<b>Condition:</b>	Pulmonary arterial hypertension (PAH)
<b>PBS Indication:</b>	Pulmonary arterial hypertension (PAH)
<b>Treatment phase:</b>	Continuing treatment (all patients)

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<p><b>Restriction Level / Method:</b></p>	<p><input type="checkbox"/> Restricted benefit  <input checked="" type="checkbox"/> Authority Required - In Writing  <input type="checkbox"/> Authority Required - Telephone  <input type="checkbox"/> Authority Required – Emergency  <input type="checkbox"/> Authority Required - Electronic  <input type="checkbox"/> Streamlined</p>
<p><b>Clinical criteria:</b></p>	<p>Patient must have received approval for initial PBS-subsidised treatment with this agent,</p> <p>AND</p> <p>Patient must have been assessed by a physician from a designated hospital to have achieved a response to their most recent course of treatment with this agent,</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised PAH agent for this condition.</p>
<p><b>Prescriber Instructions</b></p>	<p>Applications for authorisation must be in writing and must include:  (1) a completed authority prescription form; and  (2) a completed Pulmonary Arterial Hypertension PBS Authority Application - Supporting Information form which includes results from the three tests below, where available:  (i) RHC composite assessment; and  (ii) ECHO composite assessment; and  (iii) 6 Minute Walk Test (6MWT).</p> <p>Test requirements to establish response to treatment for continuation of treatment are as follows:  The following list outlines the preferred test combination, in descending order, for the purposes of continuation of PBS-subsidised treatment:  (1) RHC plus ECHO composite assessments plus 6MWT;  (2) RHC plus ECHO composite assessments;  (3) RHC composite assessment plus 6MWT;  (4) ECHO composite assessment plus 6MWT;  (5) RHC composite assessment only;  (6) ECHO composite assessment only.</p> <p>The results of the same tests as conducted at baseline should be provided with each written continuing treatment application (i.e., every 6 months), except for patients who were able to undergo all 3 tests at baseline, and whose subsequent ECHO and 6MWT results demonstrate disease stability or improvement, in which case RHC can be omitted. In all other patients, where the same test(s) conducted at baseline cannot be performed for assessment of response on clinical grounds, a patient specific reason why the test(s) could not be conducted must be provided with the application.</p> <p>The test results provided with the application for continuing treatment must be no more than 2 months old at the time of application.</p> <p>Response to a PAH agent is defined as follows:</p> <p>For patients with two or more baseline tests, response to treatment is defined as two or more tests demonstrating stability or improvement of disease, as assessed by a physician from a designated hospital.</p>

	<p>For patients with a RHC composite assessment alone at baseline, response to treatment is defined as a RHC result demonstrating stability or improvement of disease, as assessed by a physician from a designated hospital.</p> <p>For patients with an ECHO composite assessment alone at baseline, response to treatment is defined as an ECHO result demonstrating stability or improvement of disease, as assessed by a physician from a designated hospital.</p> <p>For patients aged less than 18 years, response to treatment is defined as at least one of the baseline tests demonstrating stability or improvement of disease, as assessed by a physician from a designated hospital.</p> <p>The maximum quantity authorised will be limited to provide sufficient supply for 1 month of treatment, based on the dosage recommendations in the Therapeutic Goods Administration (TGA) approved Product Information.</p> <p>A maximum of 5 repeats will be authorised.</p> <p>The assessment of the patient's response to the first and subsequent 6 month courses of treatment should be made following the preceding 5 months of treatment, in order to allow sufficient time for a response to be demonstrated.</p> <p>Applications for continuing treatment with a PAH agent should be made prior to the completion of the 6 month treatment course to ensure continuity for those patients who respond to treatment, as assessed by the treating physician.</p> <p>Patients who fail to demonstrate a response to PBS-subsidised treatment with this agent at the time where an assessment is required must cease PBS-subsidised therapy with this agent.</p> <p>The term 'PAH agents' refers to bosentan monohydrate, iloprost trometamol, epoprostenol sodium, sildenafil citrate, ambrisentan, tadalafil, and macitentan.</p> <p>PAH agents are not PBS-subsidised for patients with pulmonary hypertension secondary to interstitial lung disease associated with connective tissue disease, where the total lung capacity is less than 70% of predicted.</p>
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### 3 Background

- 3.1 At its November 2013 meeting, the PBAC noted correspondence from the Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ), recommending changes to the then current PBS restrictions for PAH agents. At the time, the PBAC considered that “such changes would all require consultation from sponsors and most would require evidence-based submissions regarding maintenance of acceptable cost-effectiveness”.
- 3.2 The DUSC analysis on PAH agents from February 2015 states: “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.”

#### **4 Current situation**

- 4.1 As at July 2015, PBS subsidy is available for the following medicines specifically for class III and/or class IV PAH: bosentan, iloprost, epoprostenol, sildenafil, ambrisentan, tadalafil, and macitentan.

#### **5 Consideration of the evidence**

##### ***Sponsor hearing***

- 5.1 There was no hearing for this item as it was a minor submission.

##### ***Consumer comments***

- 5.2 The PBAC noted and welcomed the input from individuals (9) and an organisation (1) via the Consumer Comments facility on the PBS website. The comments described the additional administrative, financial and social burdens on patients to meet the requirements for the continuing treatment restriction.
- 5.3 The PBAC noted the advice received from Pulmonary Hypertension Australia clarifying the burden of the discontinuation rules for PAH agents. The PBAC specifically noted the advice that requirement for 6 monthly assessments is a burden on patients and results in a cost to the health system and lost productivity in the workplace. The PBAC noted that this advice was supportive of the evidence provided in the submission.

##### ***Clinical trials***

- 5.4 As a minor submission, no new clinical trials were presented in the submission.
- 5.5 The basis of the minor submission's request to amend the restriction requirements was to be consistent with best clinical practice. The submission claimed that the "requirement for a patient to demonstrate stability or improvement in disease status in order to be eligible for continued treatment is not consistent with best clinical practice as outlined in international guidelines (Nice 2013)". The submission argued that the guidelines recommend sequential combination therapy in the case of inadequate clinical response to initial therapy, and do not recommend cessation of therapy and switching to another therapy.
- 5.6 The submission claimed that deterioration of a patient's health status is more likely to be due to progression of the underlying condition rather than failure of treatment.

##### ***Economic analysis***

- 5.7 As a minor submission, there was no economic comparison presented.
- 5.8 The submission noted that in November 2013, when the PBAC considered the PHSANZ's correspondence, the PBAC noted that requests to make PAH agents available for patients with functional class II disease or for use as part of combination therapy would require a submission to be made to the PBAC with evidence demonstrating the comparative clinical effectiveness and safety and

cost-effectiveness of therapy in such circumstances. While the submission did not request consideration of PBS-subsidised combination therapy as such, it did request that the restriction should allow for use in patients whose condition may have progressed, so that they may commence combination therapy with a second non-PBS subsidised agent.

### ***Estimated PBS usage & financial implications***

- 5.9 The minor submission estimated negligible financial implications to the PBS, claiming that because switching between agents is possible, it is highly unlikely that the current continuation criteria are generating cost-savings for the PBS.

## **6 PBAC Outcome**

- 6.1 The PBAC recommended the following amendments to the PBS restrictions of bosentan, epoprostenol, and macitentan:
- no changes to the initial treatment restriction;
  - that the current “continuing treatment (all patients)” restriction be replaced by the following:
    - a “continuing treatment – new patient” phase (written authority), which would retain the same criteria as the existing “continuing” treatment restriction (i.e. patient will need to demonstrate a response to the initial course of treatment); and
    - a “continuing treatment – beyond initial 48 weeks of treatment” phase (telephone authority), which would be as requested by the submission – an amended version of the current continuing treatment restriction, removing requirements to provide evidence of a response to the most recent course of treatment with the agent.
- 6.2 The PBAC considered that progression of disease in patients on PAH agents does not necessarily indicate that the therapy is no longer effective and that the biggest response will most likely be achieved in response to the initial treatment. The PBAC therefore agreed that it would be reasonable to have a first continuing treatment restriction (continuing treatment – new patient) where evidence of a response to the PAH agent must be demonstrated; and then a subsequent continuing treatment restriction (continuing treatment – beyond initial 48 weeks of treatment), which would not require further evidence of a response. That is, the PBAC recommended the removal of the requirement for a patient to have been assessed as having achieved a response to their most recent course of treatment, except where it was their first course of treatment, and thereby, the removal of the requirement for clinicians to provide results from RHC composite assessment, ECHO composite assessment and 6MWT beyond this initial assessment.
- 6.3 Noting the submission’s claim that the current PBS continuing restriction for PAH agents is inconsistent with best clinical practice, the PBAC considered that there were a number of issues around use of PAH agents that could not be assessed within the scope of this submission, including:
- lack of evidence to support cost-effectiveness of combination therapy of PAH agents, as is claimed to occur in practice (currently only one PBS-subsidised PAH agent may be used at a time); and

- lack of evidence to support cost-effectiveness for use in New York Heart Association functional class II patients; and
- difficulty in identifying the population of patients who derive the most benefit from these agents.

In this regard, the PBAC recommended that a Post-Market Review of the efficacy and cost-effectiveness of agents for the treatment of PAH, including the existing listing for class III and class IV patients, and the additional clinical place of these therapies recommended in international guidelines.

- 6.4 The submission estimated that the restriction amendment would have negligible financial impact on the PBS. The PBAC considered this claim to be reasonable.
- 6.5 The PBAC recommended that the Safety Net 20 Day Rule should apply.
- 6.6 The PBAC noted that the recommended restriction changes should also flow-on to the other PAH agents; specifically epoprostenol (Flolan Kit), ambrisentan, sildenafil, tadalafil and iloprost.
- 6.7 The PBAC noted that this submission was not eligible for an Independent Review. Independent Review is not available in response to a request to modify an existing listing.

**Outcome:**

Recommended

**7 Recommended listing**

- 7.1 Amend existing listing: restrictions to be finalised

**8 Context for Decision**

- 8.1 The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

**9 Sponsor's Comment**

Actelion welcomes the positive decision by the PBAC which will simplify the continuation of PAH treatment for patients.