

**14.3 EPOPROSTENOL, epoprostenol 500 microgram injection, vial; epoprostenol 1.5 mg injection, vial; Veletri®; Actelion Pharmaceuticals Australia Pty Ltd**

**1 Purpose of Application**

- 1.1 To request Section 100 Highly Specialised Drugs Program listing of a new brand and presentation of epoprostenol for the treatment of patients with pulmonary arterial hypertension (PAH).

**2 Requested listing**

- 2.1 Listing was requested with the same restriction, maximum quantity and repeats as currently apply to Flolan® brand of epoprostenol: <http://www.pbs.gov.au/medicine/item/5030R-5035B-5036C-5042J>
- 2.2 The PBAC considered the requested listing was appropriate.

**3 Background**

- 3.1 This brand and presentation of epoprostenol had not previously been considered by the PBAC.
- 3.2 Flolan Kit (epoprostenol sodium, powder for IV infusion 1.5 mg (base) and 500 micrograms (base) infusion administration sets) have been PBS-listed under the Section 100 (Highly Specialised Drugs Program) since 1 January 2012.
- 3.3 Veletri brand of epoprostenol was TGA registered on 28 February 2014 and is indicated for the long-term treatment, via continuous intravenous infusion, in WHO functional class III or class IV patients with:
- Idiopathic pulmonary arterial hypertension,
  - Familial pulmonary arterial hypertension,
  - Pulmonary arterial hypertension associated with the scleroderma spectrum of diseases.

**4 PBAC consideration of the evidence**

- 4.1 The PBAC noted that the application for registration of Veletri included data that established to the TGA's satisfaction that the products could be considered bioequivalent to the corresponding strengths of Flolan, sponsored by GlaxoSmithKline Australia Pty Ltd.
- 4.2 The PBAC noted that Veletri has a different 'form' of epoprostenol compared to Flolan due to differences in the mechanism of supply of the administration sets used to deliver the drug. Flolan is PBS listed as 'powder for IV infusion

with infusion administration set” whereas Veletri would be listed as injection vials, with the administration set to be provided directly to patients by the sponsor.

- 4.3 The PBAC noted the summary provided in the submission detailing the similarities and differences between Flolan and Veletri. The PBAC noted the submission’s claim that due to the differences in excipients in the powder for infusion, reconstruction requirements and distribution processes, the two epoprostenol products should not be considered substitutable by pharmacists at the time of dispensing.
- 4.4 The PBAC considered that it was reasonable to allow substitution of Veletri and Flolan by pharmacists at the time of dispensing, given the TGA finding that the two forms are bioequivalent, while noting that the rate of substitution was likely to be infrequent. The PBAC noted the advice from the sponsor that given the high level of oversight by specialists of this patient group and high level of participation by patients in managing care, it is unlikely that unintended substitution between the products would occur in practice.
- 4.5 The PBAC also noted the advice in the submission that the box size, weight, components, and branding on Flolan and Veletri boxes received from pharmacy are completely different and will be immediately recognisable to the patient.
- 4.6 Furthermore, the PBAC noted that prescribers will have the option to specify the brand of epoprostenol they wish to prescribe for their patients, and can mark the relevant box on the prescription form if they do not wish for brand substitution to occur.
- 4.7 The PBAC considered that these factors mitigated any risks that might be associated with allowing substitution.

### ***Economic analysis***

- 4.8 A formal economic analysis was not provided in the submission.
- 4.9 As Veletri is a generic equivalent (new brand) of an already listed brand of epoprostenol, the submission proposed a price for Veletri that incorporates a 16% price reduction compared with the current price for the Flolan brand of epoprostenol.

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

- 4.10 The submission claimed that there will be an increase in utilisation of epoprostenol or in associated PBS expenditure as a result of the requested listing, as Veletri will directly substitute on a 1:1 basis, for Flolan.
- 4.11 As a consequence of the statutory price reduction that applies when a new brand of a pharmaceutical item is listed on the PBS, the submission estimated

net cost savings to the PBS. The submission's estimates are presented below:

Table 2: Extent of use and expenditure on epoprostenol on the PBS from 2008/2009 to 2012/2013

Year:	2008/2009	2009/2010	2010/2011	2011/2012	2012/2013
Utilisation	191	289	355	506	602
Expenditure	\$714,724	\$1,197,079	\$1,483,021	\$2,273,157	\$2,869,199

Table 3: Projected extent of use and expenditure on epoprostenol from 2013/2014 to 2012/2013

Year:	2013/2014	2014/2015	2015/2016	2016/2017	2017/2018
Predicted growth from previous year	20.0%	12.0%	10.0%	5.0%	3.0%
Projected utilisation	722	809	890	935	963
Projected expenditure in the absence of Veletri® (assuming average cost per prescription of	\$3,441,132	\$3,855,784	\$4,241,839	\$4,456,314	\$4,589,765
Projected expenditure with the listing of Veletri® from August 2014	\$3,441,132	\$3,238,859	\$3,563,145	\$3,743,304	\$3,855,403
Savings generated as a consequence of listing of Veletri®	\$0	\$616,925	\$678,694	\$713,010	\$734,362

## 5 PBAC Outcome

- 5.1 Out of session between the March 2014 and July 2014 PBAC meetings, the Committee recommended listing the new brand of epoprostenol under the Section 100 (Highly Specialised Drugs Program). The PBAC recommended that the same restriction, maximum quantity and number of repeats as apply to the currently listed brand of epoprostenol (Flolan) should also apply to Veletri.
- 5.2 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.
- 5.3 The PBAC considered that it was reasonable to allow substitution of Veletri and Flolan by pharmacists at the time of dispensing, given the TGA finding that the two forms are bioequivalent.
- 5.4 Consistent with the current PBS-availability of epoprostenol, the PBAC recommended that this brand was not suitable for prescribing by nurse practitioners, nor should the Safety Net 20 Day Rule apply.

### Outcome:

Recommended

## 6 Recommended listing

6.1 Add new items and bioequivalence indicators (a-flag).

6.2 The restriction wording that currently applies to Flolan is reproduced here. This will be re-modelled to meet PBS listing data system requirements at the earliest opportunity.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Manufacturer	Name and
<b>EPOPROSTENOL</b>				
epoprostenol sodium powder for I.V. infusion 1.5 mg (base) infusion administration set, 1	1	0	<sup>a</sup> Flolan Kit	GK
<i>epoprostenol 1.5 mg injection, 1 x 1.5 mg vial</i>	1	0	<sup>a</sup> <i>Veletri</i>	<i>AT</i>
epoprostenol sodium powder for I.V. infusion 500 micrograms (base) infusion administration set, 1	1	0	<sup>a</sup> Flolan Kit	GK
<i>epoprostenol 500 microgram injection, 1 x 500 microgram vial</i>	1	0	<sup>a</sup> <i>Veletri</i>	<i>AT</i>

Section 100 (Highly Specialised Drugs Program)  
Private Hospital and Private Hospital

### **Authority Required**

Initial (new patients)

Application for initial PBS-subsidised treatment with epoprostenol sodium of patients who have not received prior PBS-subsidised treatment with a PAH agent and who have been assessed by a physician from a designated hospital to have:

- (a) WHO Functional Class IV primary pulmonary hypertension; OR
- (b) WHO Functional Class IV pulmonary arterial hypertension secondary to connective tissue disease.

Applications for authorisation must be in writing and must include:

- (1) a completed authority prescription form; and
- (2) a completed Pulmonary Arterial Hypertension PBS Authority Application - Supporting Information form [[www.medicareaustralia.gov.au](http://www.medicareaustralia.gov.au)] which includes results from the 3 tests below, where available:
  - (i) RHC composite assessment; and
  - (ii) ECHO composite assessment; and
  - (iii) 6MWT; and
- (3) a signed patient acknowledgment form.

Where fewer than 3 tests (see requirement 2 above) are able to be performed on clinical grounds, a patient specific reason outlining why the particular test/s could not be conducted must be provided with the authority application [see Note for test requirements].

The maximum quantity authorised will be limited to provide sufficient supply for 1 month of treatment, based on the dosage recommendations in the TGA-approved Product Information. A maximum of 5 repeats may be requested. Where fewer than 5 repeats are requested at the time of application, authority approvals for sufficient repeats to complete a maximum of 6 months of treatment may be requested by telephone by contacting Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday)

### **Authority Required**

Initial (change or re-commencement for all patients)

Application for initial PBS-subsidised treatment with epoprostenol sodium of patients with one of the following:

- (a) primary pulmonary hypertension or pulmonary arterial hypertension secondary to connective tissue disease who wish to re-commence PBS-subsidised epoprostenol sodium after a break in therapy and who have demonstrated a response to their most recent course of PBS-subsidised treatment with epoprostenol sodium; OR
- (b) WHO Functional Class IV primary pulmonary hypertension or pulmonary arterial hypertension secondary to connective tissue disease and who have received prior treatment with a PBS-subsidised PAH agent other than epoprostenol sodium; OR
- (c) WHO Functional Class III primary pulmonary hypertension or pulmonary arterial hypertension secondary to connective tissue disease and who have failed to respond to a prior PBS-subsidised PAH agent.

Applications for authorisation must be in writing and must include:

- (1) a completed authority prescription form; and
- (2) a completed Pulmonary Arterial Hypertension PBS Authority Application - Supporting Information form [[www.medicareaustralia.gov.au](http://www.medicareaustralia.gov.au)] which includes the results on which approval for the first application for PBS-subsidised PAH agent was granted; and
- (3) the date of the first application for PBS-subsidised treatment with a PAH agent; and
- (4) the results of the patient's response to treatment with their last course of PBS-subsidised PAH agent; and
- (5) for WHO Functional Class III patients, where this is the first application for epoprostenol sodium, assessment details of the PBS-subsidised PAH agent they have failed to respond to.

Where fewer than 3 tests (see requirement 2 above) are able to be performed on clinical grounds, a patient specific reason outlining why the particular test/s could not be conducted must be provided with the authority application [see Note for test requirements].

The maximum quantity authorised will be limited to provide sufficient supply for 1 month of treatment, based on the dosage recommendations in the TGA-approved Product Information. A maximum of 5 repeats may be requested. Where fewer than 5 repeats are requested at the time of application, authority approvals for sufficient repeats to complete a maximum of 6 months of treatment may be requested by telephone by contacting Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday)

### **Authority Required**

Continuing treatment (all patients)

Continuing PBS-subsidised treatment with epoprostenol sodium of patients who have received approval for initial PBS-subsidised treatment with epoprostenol sodium, and who have been assessed by a physician from a designated hospital to have achieved a response to their most recent course of epoprostenol sodium treatment [see Note for definition of response].

Applications for authorisation must be in writing and must include:

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

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.

The maximum quantity authorised will be limited to provide sufficient supply for 1 month of treatment, based on the dosage recommendations in the TGA-approved Product Information. A maximum of 5 repeats may be requested. Where fewer than 5 repeats are requested at the time of application, authority approvals for sufficient repeats to complete a maximum of 6 months of treatment may be requested by telephone by contacting Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

**Note**

Any queries concerning the arrangements to prescribe epoprostenol sodium may be directed to Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Written applications for authority to prescribe PAH agents should be forwarded to:

Medicare Australia  
Prior Written Approval of Specialised Drugs  
Reply Paid 9826  
GPO Box 9826  
HOBART TAS 7001

**Note**

The following information applies to the prescribing under the Pharmaceutical Benefits Scheme (PBS) of agents for primary pulmonary hypertension and pulmonary arterial hypertension. Where the term PAH agents appears in the following notes and restrictions it refers to bosentan monohydrate, iloprost trometamol, epoprostenol sodium, sildenafil citrate, ambrisentan and tadalafil.

Patients are eligible for PBS-subsidised treatment with only 1 of the above PAH agents at any 1 time. Eligible patients may only swap between PAH agents if they have not failed prior PBS-subsidised treatment with that agent.

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 that predicted.

The following provides some explanatory notes regarding the availability of PBS-subsidised treatment of patients with:

(a) bosentan monohydrate, of primary pulmonary hypertension or pulmonary arterial hypertension secondary to connective tissue disease, or pulmonary arterial hypertension associated with a congenital systemic-to-pulmonary shunt (including Eisenmenger's physiology), in patients with disease of WHO Functional Class III or IV severity; AND

(b) iloprost trometamol, of:

- primary pulmonary hypertension, or pulmonary arterial hypertension secondary to connective tissue disease, in patients with disease of WHO Functional Class III severity and who have failed to respond to prior PBS-subsidised treatment with an alternate PAH agent; AND
- primary pulmonary hypertension, or pulmonary arterial hypertension secondary to connective tissue disease, in patients with disease of WHO Functional Class IV severity; AND
- drug-induced pulmonary arterial hypertension, in patients with disease of WHO Functional Class III and IV severity; AND

(c) epoprostenol sodium, of:

- primary pulmonary hypertension, or pulmonary arterial hypertension secondary to connective tissue disease, in patients with disease of WHO Functional Class III severity and who have failed to respond to prior PBS-subsidised treatment with an alternate PAH agent; AND
- primary pulmonary hypertension, or pulmonary arterial hypertension secondary to connective tissue disease, in patients with disease of WHO Functional Class IV severity; AND

(d) sildenafil citrate, of primary pulmonary hypertension or pulmonary arterial hypertension secondary to connective tissue disease, in patients with disease of WHO Functional Class III severity; AND

(e) ambrisentan, of primary pulmonary hypertension or pulmonary arterial hypertension secondary to connective tissue disease, in patients with disease of WHO Functional Class III or IV severity; AND

(f) tadalafil, of primary pulmonary hypertension or pulmonary arterial hypertension secondary to connective tissue disease, in patients with disease of WHO Functional Class III severity.

From 1 April 2012, patients can access PAH agents through the PBS according to the relevant restrictions. Once these patients are approved initial treatment with 1 of these 6 drugs, they may swap between PAH agents at any time without having to re-qualify for treatment with the alternate agent. This means that patients may commence treatment with the alternate agent, subject to that agent's restriction, irrespective of the severity of their disease at the time the application to swap therapy is submitted. It also means that no new baseline measurements will be necessary. (New baselines may be submitted where the patient has failed to respond to their current treatment.)

1. Definition of primary pulmonary hypertension, drug-induced pulmonary arterial hypertension, pulmonary arterial hypertension secondary to connective tissue disease, including scleroderma, or pulmonary arterial hypertension associated with a congenital systemic-to-pulmonary shunt (including Eisenmenger's physiology).

Primary pulmonary hypertension, drug-induced pulmonary arterial hypertension, pulmonary arterial hypertension secondary to connective tissue disease, including scleroderma, or pulmonary arterial hypertension associated with a congenital systemic-to-pulmonary shunt (including Eisenmenger's physiology) are defined as follows:

(i) mean pulmonary artery pressure (mPAP) greater than 25 mmHg at rest and pulmonary capillary wedge pressure (PCWP) less than 18 mmHg; or

(ii) mPAP greater than 30 mmHg with exercise and PCWP less than 18 mmHg; or

(iii) where a right heart catheter cannot be performed on clinical grounds, right ventricular systolic pressure (RVSP), assessed by echocardiography (ECHO), greater than 40 mmHg, with normal left ventricular function.

2. Definition of WHO Functional Class III or IV disease severity.

(a) WHO Functional Class III disease severity is defined as follows:

Patients with pulmonary hypertension resulting in marked limitation of physical activity who are comfortable at rest and on ordinary physical activity experience dyspnoea or fatigue, chest pain or near syncope.

(b) WHO Functional Class IV disease severity is defined as follows:

Patients with the inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

3. Designated hospitals.

Refer to the Medicare Australia website at [www.medicareaustralia.gov.au](http://www.medicareaustralia.gov.au) for a list of designated hospitals.

4. Test requirements to establish baseline for initiation of treatment and response to treatment for continuation of treatment.

(a) Initiation of treatment.

The first written application for PBS-subsidised treatment with the first PAH agent should be accompanied by the results of a right heart catheter (RHC) composite assessment, plus an echocardiograph (ECHO) composite assessment, plus a 6 minute walk test (6MWT) to establish the patient's baseline measurements.

Where it is not possible to perform all 3 tests above on clinical grounds, the following list outlines the preferred test combination, in descending order, for the purposes of initiation of PBS-subsidised treatment:

- (1) RHC plus ECHO composite assessments;
- (2) RHC composite assessment plus 6MWT;
- (3) RHC composite assessment only.

In circumstances where a RHC cannot be performed on clinical grounds, applications may be submitted to Medicare Australia for consideration based on the results of the following test combinations, which are listed in descending order of preference:

- (1) ECHO composite assessment plus 6MWT;
- (2) ECHO composite assessment only.

Where fewer than 3 tests are able to be performed on clinical grounds, a patient specific reason outlining why the particular test/s could not be conducted must be provided with the authority application.

(b) Continuation of treatment.

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.

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. The test(s) results provided with the application for continuing treatment must be no more than 2 months old at the time of application.

#### **Note**

5. Definition of response to a PAH agent or prior vasodilator treatment.

For patients with 2 or more baseline tests, response to treatment is defined as 2 or more tests demonstrating stability or improvement of disease, as assessed by a physician from a designated hospital.

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.

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.

For patients aged less than 18 years, response to treatment is defined as at least 1 of the baseline tests demonstrating stability or improvement of disease, as assessed by a physician from a designated hospital.

6. Authority approval requirements.

(a) Initiation of PBS-subsidised treatment with a PAH agent, where the patient has not received prior PBS-subsidised treatment with that agent.

All applications for initial treatment must be made in writing, must include a completed authority prescription and must be submitted to Medicare Australia for authorisation. The total duration of initial PBS-subsidised treatment that will be approved with this first written application is up to 6 months, based on the dosage recommendations in the TGA-approved Product Information.

Bosentan only:

Approvals for the first authority prescription will be limited to 1 month of therapy with the 62.5 mg strength tablet, with the quantity approved based on the dosage recommendations in the Therapeutic Goods Administration (TGA)-approved Product Information. No repeats will be authorised for this prescription. The second authority prescription may be written for either the 62.5 mg tablet or the 125 mg tablet strengths. Where the 62.5 mg tablet strength is required, please contact Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday) for further advice. Approvals for the second authority prescription will be limited to 1 month of treatment, with the quantity approved based on the dosage recommendations in the TGA-approved Product Information, and a maximum of 4 repeats. The approved second authority prescription will be returned to the prescriber by Medicare Australia 2 weeks after the date of the approval of the first authority prescription, to allow for the uninterrupted completion of the 6 month initial treatment course. Medicare Australia will contact prescribers prior to dispatch of the second authority prescription to confirm the tablet strength required for the patient.

(b) Continuation of treatment.

Written applications for continuing treatment for patients who have demonstrated an adequate response to their current treatment must be submitted to Medicare Australia for authorisation every 6 months. Approvals will be limited to provide sufficient supply for up to a maximum of 6 months of treatment, based on the dosage recommendations in the TGA-approved Product Information.

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. 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.

(c) Swapping between PAH agents.

For eligible patients, applications to swap between these 6 drugs must be made under the relevant initial treatment restriction. Patients should be assessed for response to the treatment they are ceasing at the time the application to swap therapy is being made. Patients who fail to demonstrate a response or for whom no assessment results are submitted with the application to swap therapy may not re-commence PBS-subsidised treatment with the drug they are ceasing.

It is important that patients are assessed for response to every course of treatment approved within the timeframes specified in the relevant restriction, in order to maximise the choice of treatment.

To avoid confusion, applications for patients who wish to swap to an alternate treatment should be accompanied by the previously approved authority prescription, or remaining repeats, for the treatment the patient is ceasing.

(d) Cessation of treatment — bosentan patients only.

Patients who fail to demonstrate a response to PBS-subsidised bosentan monohydrate treatment at the time where an assessment is required must cease PBS-subsidised bosentan monohydrate therapy.

For patients ceasing treatment, approval will only be granted to provide sufficient supply of the 62.5 mg tablet strength to allow gradual dose reduction over a period of no more than 1 month duration. Prescribers should telephone Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5

p.m. EST Monday to Friday) to receive authorisation for this final supply and to ensure no unintended break in treatment occurs.

7. Re-treatment with a PAH agent.

Patients who do not respond to treatment are not eligible to receive further PBS-subsidised treatment with that agent under any circumstances.

8. Further information.

A tabulated representation of the above information and the restriction can be obtained from the Medicare Australia website at [www.medicareaustralia.gov.au](http://www.medicareaustralia.gov.au).

## **7 Context for Decision**

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

## **8 Sponsor's Comment**

Actelion Pharmaceuticals Ltd welcomes the decision by the PBAC to make Veletri available on the PBS.