

For medicines covered by the PAH Panel, this document sets the rules under which an applicant may apply for funding. Below we have set out how we propose to change the current document. Additions are underlined, and deletions are in strikethrough.

ELIGIBILITY CRITERIA FOR PULMONARY ARTERIAL HYPERTENSION THERAPY

These guidelines are intended to assist relevant practitioners in gauging which patients are likely to be approved for pulmonary arterial hypertension (PAH) treatments. ~~In view of the complexity of pulmonary arterial hypertension diagnosis, classification and severity assessment, each application is thoroughly evaluated by the PAH Panel to determine the appropriateness of pulmonary vasodilator treatment. Five treatments are currently funded for PAH. Of these, applications for two – sildenafil and bosentan – are through standard Special Authorities (SA), while the other three – ambrisentan, iloprost, and epoprostenol – are through Panel applications.~~

This document describes the general funded treatment pathway, including treatments both through regular Special Authorities and Panel applications. For sildenafil and bosentan, no application to the Panel is necessary. If a patient is seeking a treatment regimen that includes at least one of sildenafil and bosentan as well as a medicine covered by the Panel, please make a Panel application as well as completing a regular Special Authority form. Applications to the Panel may be made by a relevant specialist or a medical practitioner on the recommendation of a relevant specialist.

Please note that the pharmaceuticals covered by these access criteria have different registered indications, and that some of the criteria included here are Unapproved Indications. If clinicians are intending to prescribe any of these pharmaceuticals for an Unapproved Indication, they should be aware of and comply with their obligations, including those set out in rule ~~4.6~~5.5 of the Pharmaceutical Schedule.

All requested ~~tests studies~~ should be carried out in line with the relevant professional guidelines. Patients with pulmonary arterial hypertension who meet the following criteria may be eligible for initiation of pulmonary arterial hypertension treatment based on current clinical evidence.

The following treatments may be subsidised by application to the PAH Panel:

Category	Treatment
Endothelin receptor antagonists	Ambrisentan (Volibris) Bosentan (Tracleor)
Phosphodiesterase type 5 inhibitors	Sildenafil (Viagra)
Prostacyclin analogues	Iloprost (Ventavis)

MONOTHERAPY

A patient's first treatment must be monotherapy. A patient is expected to start on sildenafil monotherapy, unless they are:

- a) A child with idiopathic PAH or PAH secondary to congenital heart disease, in which case they may start with bosentan monotherapy.
- b) Intolerant of or contraindicated to sildenafil, in which case they may have bosentan monotherapy, or may apply to the Panel for ambrisentan, iloprost, or epoprostenol monotherapy. (Epoprostenol monotherapy may only be applied for in patients meeting the criteria described further below.)

A patient will need to complete three months of a monotherapy treatment before combination treatments will be considered.

DUAL THERAPY

To be eligible for dual therapy, a patient must either have:

- Tried a monotherapy for three months with no response, or
- Have deteriorated while on a monotherapy, as determined by:
 - Clear evidence of deterioration in right heart cardiac catheterisation measures; or
 - 15% deterioration in two 6 minute walk tests (6MWTs) done at least two weeks apart; or
 - NYHA/WHO functional class IV (the NYHA/WHO functional classification for PAH replicated on page 4).

For patients who are tolerant of sildenafil, one of the two agents must be sildenafil. Use of epoprostenol is restricted as described further below. Beyond that, clinicians may apply for any dual combination.

If a patient does not respond to a particular dual combination or deteriorates as described above, the clinician may apply for another dual therapy, noting the above restrictions still apply.

TRIPLE THERAPY

A patient on the lung transplant waiting list may apply for triple therapy. Any combination may be applied for, as long as sildenafil-tolerant patients include sildenafil as one of the three agents, and epoprostenol is only used as described below.

A patient who meets the following criteria (which are the same as the criteria for epoprostenol below) may also apply for triple therapy, however if they are not on the lung transplant list then the triple therapy must consist of sildenafil, bosentan, and any one other agent.

1. Patients presenting acutely with idiopathic pulmonary arterial hypertension (IPAH) in New York Heart Association/World Health Organization (NYHA/WHO) Functional Class IV; or
2. Patients deteriorating rapidly to NYHA/WHO Functional Class IV who may be lung transplant recipients in the future, if their disease is stabilised; or
3. Patients with PAH associated with the scleroderma spectrum of diseases (APAHSSD) who have no major morbidities and are deteriorating despite combination therapy, or
4. For use as a bridge to transplant for patients with pulmonary arterial hypertension who are on the active waiting list for lung transplantation.

USING EPOPROSTENOL WITHIN ONE OF THE ABOVE THERAPIES

Epoprostenol may only be used when patients meet one of the following criteria:

1. Patients presenting acutely with idiopathic pulmonary arterial hypertension (IPAH) in New York Heart Association/World Health Organization (NYHA/WHO) Functional Class IV; or
2. Patients deteriorating rapidly to NYHA/WHO Functional Class IV who may be lung transplant recipients in the future, if their disease is stabilised; or
3. Patients with PAH associated with the scleroderma spectrum of diseases (APAHSSD) who have no major morbidities and are deteriorating despite combination therapy, or
4. For use as a bridge to transplant for patients with pulmonary arterial hypertension who are on the active waiting list for lung transplantation.

Epoprostenol may be used as monotherapy or as part of a dual or triple therapy, provided all other conditions are met.

Patients eligible for approval of treatment by the PAH Panel

Where an application is put to the Panel for consideration (instead of through the standard Special Authorities), the following conditions must be met:

1. The patient must have a diagnosis of pulmonary arterial hypertension with the following WHO (Venice) clinical classifications:
 - **Group 1**
 - Idiopathic;
 - Familial;
 - Associated with:
 - Connective tissue disease;
 - Congenital systemic pulmonary shunts;
 - Portal hypertension;
 - HIV infection;
 - Drugs and toxins;
 - Other;
 - Associated with significant venous or capillary involvement:
 - Pulmonary veno-occlusive disease (PVOD);
 - Pulmonary capillary haemangiomatosis (PCH);
 - Persistent pulmonary hypertension of the newborn (PPHN) including:
 1. persistent pulmonary hypertension associated with premature/neonatal severe chronic lung disease or congenital diaphragmatic hernia
 2. infantile severe chronic lung disease where there is supportive evidence that the pulmonary vascular resistance had never normalised
 - **Group 4**
 - Pulmonary arterial hypertension due to thrombotic and/or embolic disease only)
 - **Group 5**
 - Miscellaneous group
 - E.g. sarcoidosis, histiocytosis X and lymphangiomatosis

Patients with PAH classified as group 2 or 3 are not eligible for subsidised treatment.

- **Group 2** – pulmonary hypertension associated with left heart disease
- **Group 3** – pulmonary hypertension associated with respiratory diseases and / or hypoxaemia.

Lung function tests and cardiac function tests must be supplied with the ~~initial~~first Panel application. ~~For children under 10 years old, funding of bosentan or sildenafil for children with idiopathic pulmonary arterial hypertension or pulmonary hypertension secondary to congenital heart disease will be considered using the data provided according to the application forms for children less than 10 years.~~

2. The patient must ~~have~~be in NYHA/WHO functional class II, III, or IV. ~~For patients who are functional class II, applications will be considered in cases where there is clear evidence of disease progression (defined as a deterioration in performance of the 6MWT or deterioration in haemodynamic variables) despite current therapy.~~

Patients who are functional class I are not eligible for subsidised treatment.

New York Heart Association / World Health Organization Functional Classification of Pulmonary Hypertension	
Class I:	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near syncope.
Class II:	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near syncope.
Class III:	Patients with pulmonary hypertension resulting in pronounced limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
Class IV:	Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients have manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

3. Right cardiac catheterisation data¹ must be supplied with the application. If cardiac catheterisation is contraindicated, a letter of explanation is required. Unequivocal, significant evidence of raised pulmonary arterial pressure, in the absence of significant left heart disease, must be demonstrated.
 - The patient must have a pulmonary capillary wedge pressure (PCWP) \leq 15 mmHg (patients with a PCWP between 15 mmHg and 18 mmHg may be considered at the Panel's discretion).
 - The patient must have a mean pulmonary artery pressure (PAPm) $>$ 25 mmHg unless the patient is peri Fontan repair (see below).

¹ Grossman, W (Ed). Cardiac Catheterization and Angiography, 3rd ed, Lea & Febiger, Philadelphia 1986

- The patient must have a pulmonary vascular resistance (PVR) of:
 - > 3 Wood Units; or
 - > 240 International Units (dyn s cm⁻⁵)
 - An assessment of vasoreactivity has been carried out using iloprost, adenosine or nitric oxide. Where this assessment has not been carried out, applicants must provide reasons for this. (Vasoreactivity studies are not mandatory in patients with severe PAH (functional class IV or right atrial pressure > 12 mmHg or Cardiac Index < 2 L/min/m²) or PAH associated with connective tissue disease.)
 - Where the patient has been shown to be vasoreactive (defined as a fall in mean PAP of greater than or equal to 10mmHg to less than 40mmHg with either an increase or no change in cardiac index), evidence of an adequate therapeutic trial of calcium channel blockers for three to six months must have been undertaken, followed by re-catheterisation demonstrating evidence of haemodynamic progression. (Due to the negative inotropic effects of CCBs, a trial of CCBs is not required in patients with severe disease as defined above.)
 - For children peri Fontan repair, haemodynamic data is required and formal cardiac catheterisation should be considered at a clinically appropriate stage of the patient's management. Due to the presence of a non-pulsatile circuit a mean pulmonary artery pressure (PAPm) < 25mmHg would be acceptable.
4. Persistent pulmonary hypertension of the newborn associated with severe chronic lung disease (CLD) or congenital diaphragmatic hernia (CDH).
- The application must include an inpatient management summary, admission history, echocardiogram, and short and long term management plan (including weaning plan).
 - Cardiac catheter should be considered for patients with CDH or CLD at a clinically appropriate stage of the patient's management where treatment is required for 12 months or more.

Treatment selection

Initial treatment:

~~Patients who have not previously been treated with any of these agents would generally be expected to start treatment with sildenafil.~~

~~Children with idiopathic pulmonary arterial hypertension or pulmonary hypertension secondary to congenital heart disease would generally be expected to start treatment with bosentan.~~

~~NYHA WHO functional class IV patients who have been stabilised in hospital on iloprost would be able to receive iloprost in the community for a period of time to allow transition to sildenafil monotherapy, if clinically appropriate.~~

Change of treatment:

~~For children previously approved for funded sildenafil for the treatment of idiopathic pulmonary arterial hypertension or pulmonary hypertension secondary to congenital heart disease clinicians may apply to switch the child to bosentan.~~

~~For indications other than those above, where sildenafil is not tolerated due to side effects clinicians may apply for monotherapy with bosentan, ambrisentan or iloprost.~~

~~Where the patient has not responded to sildenafil monotherapy, clinicians may apply for alternative monotherapy within 6 months of treatment initiation.~~

~~Patients eligible for renewal of Special Authority~~

~~Renewal applications must be submitted to the PAH Panel upon expiry of the initial approval period.~~

~~Treatment selection~~

~~Renewal of treatment (stable patients):~~

~~Patients who are stable or improve on PAH therapy will be considered for renewal of special authority.~~

~~Escalation of treatment:~~

~~Eligibility for combination therapy for patients stable on treatment for at least six months who then deteriorate shall be determined by:~~

~~Clear evidence of deterioration in right heart cardiac catheterisation measures; or~~

- ~~• 15% deterioration in two 6MWTs done at least two weeks apart; or~~
- ~~• NYHA/WHO functional class IV.~~

~~Where patients show signs and symptoms of deterioration, and escalation of treatment is requested, a repeat right heart cardiac catheter is mandatory, except if the cardiac catheter is contraindicated, when a letter of explanation must be provided for the Panel to consider.~~

~~Patients who have failed to respond to two monotherapies within the first six months of treatment may be eligible for combination therapy.~~

~~Combination bosentan/iloprost or ambrisentan/iloprost may be considered for adult patients who cannot tolerate a sildenafil regime.~~

~~Combination sildenafil/bosentan/iloprost therapy will not be approved.~~

~~Combination sildenafil/ambrisentan/iloprost therapy will not be approved.~~