**Pharmaceutical Benefits Scheme**

**Post-market Review of**

**Medicines to treat Pulmonary Arterial Hypertension**

**Term of Reference 5**

**Final Report**

**November 2018**

**Contents**

Abbreviations 3

ToR 5: Cost-effectiveness 4

5.1 Key findings for Term of Reference (ToR) 5 4

5.2 Consider Reviewing the Cost-effectiveness of PAH medicines according to current PBS Listings 5

5.2.1 Summary of issues highlighted in ToR 1-4 that potentially impact the cost‑effective use of PBS listed medicines for PAH. 5

5.2.2 Summary of cost- effectiveness models previously considered by PBAC for the current PBS listed PAH medicines 5

5.2.3 Stakeholder Comments 9

5.3 Consider Reviewing the Cost-effectiveness of PAH medicines in WHO functional Class II 10

5.3.1 Summary of issues highlighted in ToR 1-4 that potentially impact the cost‑effective use of PBS listed PAH medicines 10

5.3.2 Summary of cost- effectiveness models for PAH assessing treatment of patients in WHO FC II 11

5.3.3 Consumer Comments 11

5.4 Consider Reviewing the Cost-effectiveness of treating patients in WHO functional Class III and IV with combinations of PAH medicines 12

5.4.1 Summary of issues highlighted in ToR 1-4 that potentially impact the cost‑effective use of PBS PAH medicines 12

5.4.2 Summary of cost- effectiveness models for PAH assessing patients in WHO FC III and IV treated with combination therapy 14

References 16

# Abbreviations

|  |  |
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| **Abbreviation** | **Full Name / Wording**  |
| CDEC | Canadian Drug Expert Committee |
| ERA | Endothelin receptor antagonist |
| EQ-VAS | EuroQol-visual analogue scales |
| FC | Functional class |
| F2 | Formulary 2  |
| GRADE | Grading of Recommendations Assessment, Development, and Evaluation |
| ICER | Incremental cost effectiveness ratio |
| LPH | Living with Pulmonary Hypertension Questionnaire |
| MLHF | Minnesota Living with Heart Failure Questionnaire |
| MM | Morbidity or mortality |
| NICE | National Institute for Health and Clinical Excellence |
| PAH | Pulmonary arterial hypertension |
| PAH-CTD | PAH associated with connective tissue disease |
| PBAC | Pharmaceutical Benefits Advisory Committee |
| PBS | Pharmaceutical Benefits Scheme |
| PDE-5 inhibitor | Phosphodiesterase type 5 inhibitor |
| PVR | Pulmonary vascular resistance |
| RCT | Randomized controlled trial |
| QoL | Quality of life |
| sGC stimulator | Soluble guanylate cyclase stimulator |
| ToR | Term(s) of Reference |
| WHO | World Health Organization |
| 6MWD | Six-minute walk distance |

# ToR 5: Cost-effectiveness

Following ToR 1-4, consider reviewing the cost-effectiveness of existing PBS listings for PAH medicines, and in treatment of WHO functional class II and combination treatment in class III and class IV patients.

## 5.1 Key findings for Term of Reference (ToR) 5

* There was no new clinical evidence identified for the use of PAH medicines in monotherapy reporting mortality or quality of life outcomes to inform a new cost-effectiveness assessment of current Pharmaceutical Benefits Scheme (PBS) listed PAH medicines.
* The utilisation review of PBS data indicated that PAH medicines are being used as the sole PBS subsidised PAH therapy, consistent with their current restrictions.
* Overall the use of endothelin receptor antagonists (ERAs) is likely to be beneficial for patients in World Health Organization (WHO) functional class (FC) II, however there is considerable uncertainty whether the use of phosphodiesterase type 5 (PDE-5) inhibitors and ''''''''''''''' ''''''''''''''''' ''''''''''''' ''''''''''' ''''''''''''''''''''''' ''' ''''''''''''''''''', and there was no evidence found to support monotherapy use of prostanoids in patients presenting in WHO FC I or II.
* While there is trial evidence to support dual PAH therapy over monotherapy, it varies according to the various combinations, and is overall inconclusive for the sub-groups of patients treated in WHO FC III and IV. However, these sub-groups were small and potentially underpowered to report significant differences between treatment arms.
* Several trials '''''''''''''''''''''' HAN 2017, COMBI'' ''''''''''''''''') measured change in quality of life in patients (FC II-IV) treated with combinations of: ''''''''' ''''''' ''''''''''' '''''''''''''''''''; ERA and prostanoids; and ''''''' ''''''''''''' '''' '''''''' '''''''''''''''''''. All trials reported significant improvements in quality of life in patients treated with combination therapy compared to monotherapy.
* There was no evidence identified in the systematic review of PBS listed PAH medicines that reported on the effectiveness of triple combination therapy compared to dual combination therapy.
* PBAC has not received a submission requesting subsidised access to PAH specific medicines for patients presenting in WHO FC II.
* The PBAC has considered a submission for selexipag in combination with an ERA and/or PDE-5 inhibitor. PBAC has rejected this submission on two occasions due to high and uncertain cost effectiveness in the requested dual and triple combinations.
* Due to patent expiry and movement to Formulary 2 (F2), the original Pharmaceutical Benefits Scheme (PBS) prices for bosentan, epoprostenol and sildenafil are now lower than when originally listed and are likely to fall further due to PBS price disclosure mechanisms.
* Cost-effectiveness may be acceptable for some dual combination therapies involving currently listed PBS PAH medicines that have moved to F2, given they are now listed at lower prices than their original cost-effective price in monotherapy. Noting non-inferior safety and some clinical benefit would need to be accepted, as combination therapy would result in an additional net cost to the PBS.

## 5.2 Consider Reviewing the Cost-effectiveness of PAH medicines according to current PBS Listings

### 5.2.1 Summary of issues highlighted in ToR 1-4 that potentially impact the cost‑effective use of PBS listed medicines for PAH.

The evidence on the efficacy and safety of monotherapy for patients in WHO FC III and IV was reviewed in ToR 4. This review found **no** new evidence concerning the efficacy and safety of PAH medicines beyond that already considered by the Pharmaceutical Benefits Advisory Committee (PBAC) for each PAH medicine currently listed on the PBS.

The utilisation analyses of PBS data presented in ToR 2 confirmed that that almost all use of PBS subsidised PAH medicines has been for monotherapy in accordance with PBS restrictions. Analyses of two patient registry sub-populations indicates that around half the treated PAH populations are receiving combinations of PAH medicines; however these combinations are provided or accessed through other sources than the PBS.

### 5.2.2 Summary of cost- effectiveness models previously considered by PBAC for the current PBS listed PAH medicines

Bosentan was the first PAH specific medicine listed on the PBS in 2004. The PBAC considered two major submissions from the sponsor of bosentan in December 2002, June 2003, and two minor submissions in September 2003 and December 2003. The following is a summary of the submissions and the final PBAC recommendation.

All other PAH medicines listed on the PBS have been listed on the basis of a cost minimisation comparison to bosentan. Thus, the original economic analysis for bosentan compared to usual care (placebo) was the only cost-effectiveness assessment considered by the PBAC for the all currently listed PAH medicines. The following information is provided in confidence to PBAC based on the original submissions and PBAC Minutes for bosentan.

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**National Institute for Health and Clinical Excellence cost effectiveness review of PAH medicines**

In 2005 the National Institute for Health and Clinical Excellence (NICE) began a health technology assessment of epoprostenol, iloprost, bosentan, sitaxentan and sildenafil for the treatment of PAH in adults[[1]](#endnote-1). However, this assessment was not fully completed and was removed from the work program in March 2009. In 2009, this assessment was published as a systematic review and economic evaluation of the clinical and cost-effectiveness of epoprostenol, iloprost, bosentan, sitaxentan and sildenafil for pulmonary arterial hypertension within their licensed indications by Chen et al (2009)[[2]](#endnote-2).

This review concluded that all five PAH medicines, when added to supportive care, were found to be more effective than supportive care alone in populations that included patients of mixed FC and types of PAH. The evidence at that time did not allow for adequate comparisons between medicines, nor for the use of combination therapy. Independent economic evaluations (from sponsors) suggest that bosentan, sitaxentan and sildenafil may be cost effective by standard thresholds and that iloprost and epoprostenol may not. The findings suggest there is different cost-effectiveness across the oral medicines; however this required further investigation as the current analysis was not designed to directly compare the individual medicines.

There were a number of uncertainties raised by the assessment group on the economic modelling of these medicines. These uncertainties were mainly due to the lack of long term data from RCTs and the paucity of data stratified according to PAH sub-types and WHO FC. The incremental cost effectiveness ratios (ICERs) for the oral agents were also considered highly sensitive to the price of epoprostenol, as epoprostenol is considered the treatment of choice for patients in WHO FC IV.

### 5.2.3 Stakeholder Comments

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* A stakeholder group stated that cost effectiveness of PAH medicines should be assessed with regard to patient outcome measures focusing on quality of life with a lesser emphasis on mortality, and argues that early treatment with combination therapy is cost effective and reduces hospitalisation.
* A health practitioner noted that while PAH drugs are effective, the heterogeneity of the patient groups, the variable response within groups and the relatively rare set of diseases make it impossible to produce robust cost-effectiveness data to guide funders in developing clearly proven acceptable funding strategies.

## 5.3 Consider Reviewing the Cost-effectiveness of PAH medicines in WHO functional Class II

### 5.3.1 Summary of issues highlighted in ToR 1-4 that potentially impact the cost‑effective use of PBS listed PAH medicines

The systematic literature review presented in ToR 4 of this report assessed the clinical efficacy and safety of monotherapy in patients presenting in WHO FC l and ll. The review reports the following according to PAH medicine class.

**ERAs versus placebo**: Four RCTs were identified that assessed a range of patient outcomes when treated with ERAs versus placebo. All four RCTs ''''''''''''' '''''''''''' ''' ' '''' '''''''''''''''''''''' '''''''''''''''''' '''''''''''''''''''''' ''''''''''' '''''''''''''''' ''''''''''''' '''''''' ''''''''' ''''''''''''''''''''''' '''''''''''''' '''''''''''''''''''' ''''''''''' ''''''''''''' ''''''''''''''''''''' '''''''' ''''''''' '''''''''''' '''''''' ''''''''''''''''''' '''''''''''''''''' ''''''''''''''' ''''''''''''''''' '''''''''''' '''''''' '''''''' ''''''' ''' ''''''''''''''''''''' '''''''''''''''''' ''''''' ''''''''''''' '''''''''' ''''' ''''' ''''' ''''''''''''''''''' ''''''''''''''''''' ''''''''''''''''' ''''''''''''''''' ''''' ''''''' ''''' ''''''''''''''' ''''''''' '''''''''''' ''''''''''''''''' Two RCTs measured change in WHO FC and found significantly more patients improved in WHO FC while being treated with an ERA. Three RCTS reported on change in the six-minute walk distance (6MWD) and found significantly more patients had a clinically meaningful reduction in 6MWD while on ERA compared to placebo. One RCT reported patients taking an ERA had a larger mean improvement in pulmonary vascular resistance (PVR) compared to placebo. There was no significant between ERAs for the outcomes of clinical worsening, all-cause mortality and 6MWD.

**PDE-5 inhibitors versus placebo**: There were two RCTs (PHIRST, SUPER-1) and two cohort studies (Sun 2013, Sastry 2007) identified that compared PDE-5 inhibitors to placebo in patients presenting in WHO FC I or II. Two cohort studies reported that fewer patients died when treated with PDE-5 inhibitors, however these results were not statistically significant. One of two trials assessing change in 6MWD reported a clinically important improvement in patients taking PDE-5 inhibitor compared to placebo. There was no difference in effectiveness between PDE-5 inhibitors.

**Prostanoids versus placebo:** There was no evidence available to assess the efficacy and safety of prostanoids in patients presenting in WHO FC I or II.

**sGC stimulator versus placebo**: One RCT ''''''''''''''''''''''' was identified that reported on a range of patient outcomes. In this trial, '''''''''''''''''''' '''''''''' ''''''''''''''' ''''''''''''''''''''''' '''''''''''' ''''''''''''''' ''''''''''''''''''' '''''''' '''''''''''''''''''' '''''''''' '''''''''''''''' '''''''''''' ''' ''''''' ''''''''''''''''''' ''''''' ''' '''''''''''' '''''''''''' ''''''''''''''''''''''''''' '''' '''''''''''' ''''' ''''''' '''''''''''' ''''''' ''''''''''''''''''' '''''''''''''' '''''''''''''''''''' '''''''''''' ''''''' ''''' ''''''''''''''''''''' ''''''''''''''''''' ''''''''''''''''''' '''' ''''''''''''''' ''''''''''''''''''' ''''''''''''''''''''''''' '''' '''''''''''''' '''' '''''''''''' ''''''''''''' ''''''''' '''''''' '''''''''''''''''''' ''''''''''''''''''''' ''''' '''''''''''''''

In summary, the use of ERAs is likely to be beneficial for patients in WHO FC II, however there is considerable uncertainty whether the use of PDE-5 inhibitors ''''''' ''''''' ''''''''''''''''''''''' is beneficial, and there was no evidence found to support the use of prostanoids in patients presenting in WHO FC I or II.

#### Utilisation of PAH medicines in WHO FC II

Registry data from the Pulmonary Hypertension Society of Australia and New Zealand indicates that approximately 20% of patients in the PAH cohort (those alive and receiving medication in 2017) were diagnosed or presented to PAH centres with symptoms classified in WHO FC II. The majority (67%) of patients entered the cohort with WHO FC III symptoms and 6% with WHO FC IV symptoms. Information on WHO FC at time of cohort entry was not available in 6.8% of patients.

The utilisation of PBS medicines cannot be determined according to WHO FC and the both registry data analyses did not provide specific information on the extent of patients being initiated to PAH therapy in WHO FC II.

### 5.3.2 Summary of cost- effectiveness models for PAH assessing treatment of patients in WHO FC II

PBAC has not received a submission requesting subsidised access to PAH specific medicines for patients presenting in WHO FC II. There are international cost effectiveness reviews addressing cost-effectiveness of PAH medicines in patients presenting in WHO FC II. The Canadian Drug Expert Committee (CDEC 2015) made the following recommendations in the CADTH Therapeutic Review Report[[3]](#endnote-3):

* that sildenafil or tadalafil be the preferred initial therapy for adult patients with FC II and III PAH and
* that add-on therapy should be used in adult PAH patients who are unable to achieve disease control with a single drug.
* CDEC could not make a specific recommendation pertaining to subgroups of patients (based on disease severity or other disease characteristics) who may benefit more from specific drugs or combinations of drugs based on the evidence reviewed.

### 5.3.3 Consumer Comments

* Some consumers suggested that earlier treatment and combination therapy led to better health outcomes and questioned why treatment is not available for FC II patients whose health is only going to deteriorate. They also suggested that earlier treatment could be more cost-effective.

## 5.4 Consider Reviewing the Cost-effectiveness of treating patients in WHO functional Class III and IV with combinations of PAH medicines

### 5.4.1 Summary of issues highlighted in ToR 1-4 that potentially impact the cost‑effective use of PBS PAH medicines

The systematic review of PAH medicines presented under ToR 4 identified trials comparing dual therapy versus monotherapy involving PBS listed PAH medicines. The quality of this evidence varied and was mainly conducted in mixed populations of varying WHO FC and PAH aetiologies.

#### Combination therapy including ERA and PDE-5 inhibitors

Four RCTs in total assessed the combinations of an ERA added to PDE-5 inhibitors ''''''''''''''' ''''''''''''''''' '''' ''''''''''''''''''' ''''''' '''''''''''''''''''''', and two of these presented results for the sub-groups for WHO FC III and IV patients '''''''''''''''''''' ''''''''''''''''''''' ''''''''''' '''''''' '''''''''' ''''''''''''''' ''''' '''''''''''''''''''' ''''''''''''''''''''' '''''''''''''''''''' '''''''''''''''''' ''''''''''''''''''''' ''''''''''''''' '''''''' '''''''''''''''''''''''''''' ''' '''''''''''' '''' '''''''''''''' '''''''''''''' '''''''''''''''''''' ''''''''''''' '''' ''''''''''''' One of these trials (SERAPHIN) reported a significantly larger mean improvement in quality of life (SF-36 physical component) for patients on combination therapy; however this result was for the total study population that also included patients in WHO FC II. The fourth trial (AMBITION) enrolled treatment naive patients to initial combination therapy versus monotherapy. Overall there were no statistically significant differences in the effectiveness of treatment when patients received initial combination therapy or sequential combination therapy.

Five RCTs in total assessed the combination of PDE-5 inhibitor added to ERA (PHIRST, Mainguy 2013, Vissa 2017, Zhuang 2014, AMBITION), and two of these RCTs (PHIRST and Zhuang) provided results for the sub-group of patients in WHO FC III and IV. For patients in the WHO FC III/IV sub-groups there was no clinically meaningful difference in 6MWD between those treated with sequential combination therapy versus monotherapy. The results for the trials where all participants were included did show clinically significant improvements for number of hospitalisations, change in WHO FC and haemodynamic parameters. The safety of PDE-5 inhibitor added to and ERA appears non-inferior to ERA monotherapy, although there is a possible safety concern in terms of an increased number of severe adverse events for the sub-group of patients with PAH associated with connective tissue disease (PAH-CTD) who were taking combination therapy.

#### Combination therapy including ERA and prostanoids

Two RCTs enrolled treatment naïve patients in WHO FC III or IV and compared clinical outcomes between those initiated to combinations of an ERA and prostanoid versus prostanoid monotherapy (HAN 2017, BREATHE-2). Overall, the evidence from these trials was inconclusive to support dual therapy being superior to monotherapy with a prostanoid. One small study (Han 2017) of low quality reported a larger mean improvement in quality of life (MLHF) in patients initiated to combination therapy.

Two more RCTs were identified that compared combination therapy in patients who added a prostanoid to existing ERA therapy versus continuing monotherapy with an ERA (COMBI, STEP). For patients on combination therapy: significantly more improved their WHO FC; had larger mean improvements in haemodynamic parameters; and reported larger improvements in quality of life (EQ-VAS). Noting these were studies that were GRADED low to very low quality.

#### Combination therapy including ERA and sGC stimulators

One RCT '''''''''''''''''''' compared the effectiveness of adding a sGC stimulator to patients treated with or without an ERA or prostanoid. Only 14% of enrolled patients were in WHO FC III/IV and therefore the trial provided limited evidence to support this particular combination. '''''''''''' ''''' '''''''' '''''''''''''''' '''' '''''''' '''''''' '''''''''' '''''''''''''' ''''''''' ''''''''''''''''''''' '''''''''''''''' '''''' '''''''''''''''''''''' ''''''''''' '''''''''' ''''''''''''''''''''''''''''' '''' '''''''' ''''''''''''' '''' '''''' '''''''''''''' ''''''''' ''''''' '''''' '''''''''''''''''' ''''''' '''''''''''''''''' ''''''''' ''''''''''''''

#### Combination therapy including PDE-5 inhibitors and prostanoids

One RCT (PACES-1) compared the effectiveness of adding PDE-5 inhibitor to a prostanoid versus continuing monotherapy with a prostanoid alone. There were no separate results for patient with PAH WHO FC III and IV. For patients treated with combination therapy significantly fewer died from all causes and significantly fewer experienced clinical worsening and this evidence was GRADED high quality.

#### Combination therapy including PDE-5 inhibitors and sGC stimulators

One RCT (PATENT-PLUS) compared the effectiveness of sGC stimulator added to a PDE-5 inhibitor versus continuing monotherapy with PDE-5 inhibitor alone in PAH patients classified WHO FC III and IV. This trial reported no statistically significant differences in any of the clinical outcomes for efficacy or safety between patients treated with combination therapy and monotherapy, noting the trial was small, possibly underpowered and GRADED low quality evidence.

#### Combination therapy involving prostanoids and sGC stimulators

One RCT '''''''''''''''''''' reported on the effectiveness of adding a sGC stimulator to a prostanoid versus continuing therapy with a prostanoid alone'' '''''''' ''''''''''' '''''''''''' '''''''' ''''''''''''''' ''''' ''''''''''''''''''''''' '''''''''''''''' ''''''''''''''''' ''' '''''''''' '''''''''''''''''''''''' '''' ''''''''''''''' '''''''''''''''''''''''''''' '''''''''''''''''''''' '''''''' '''''''''''''' '''' '''''' ''''''''''''''' ''''''''' ''''''''''''''''''''' ''''' '''''''''''''''''''''''''''' ''''''''''' ''''''''' ''''' ''''''''''''' '''''''''''''''''' ''''''''''''''''''' '''''' '''''''''''''' ''' '''''''''' ''''' ''' '''' ''''' '''''''' '''''''' '''''''''''''''''' ''''''' '''''''''''''''' '''''''''''''''' '''' ''''''' ''''''''''''''

#### Triple combination therapy versus dual combination therapy for PAH

There was no comparative evidence found assessing the effectiveness and safety of triple combination therapy with PBS listed PAH medicines relative to dual combination therapy.

#### Utilisation of PAH medicines in combination therapy

Evidence provided from two Australian patient registries suggest that approximately 40% of all patients with PAH are currently treated with dual combinations of PAH medicines and 10% with triple combinations. Currently the additional medicines are not being subsidised through the PBS but other sources such a hospitals, compassionate access programs and privately purchased prescriptions.

5.4.2 Summary of cost- effectiveness models for PAH assessing patients in WHO FC III and IV treated with combination therapy

PBAC has received two submissions requesting PBS listing of selexipag for use in combination with an ERA and/or a PDE-5 inhibitor – both PBS subsidised therapies. The following is taken from the public summary documents following PBAC consideration in March 2016 and March 2017.

In March 2016 the PBAC considered a major submission for the listing of selexipag[[4]](#endnote-4) for second and third line treatment of idiopathic PAH, drug or toxin induced PAH, hereditable PAH, PAH secondary to connective tissue disease, congenital heart disease with systemic-to-pulmonary shunt or HIV infection in patients in WHO FC III-IV PAH stabilised on a background therapy with an ERA and/or a PDE-5 inhibitor, but who have not achieved physician-directed treatment goals. The proposed listing also included initial combination treatment.

The submission presented clinical evidence from the GRIPHON trial: Sitbon et al, 2015, a randomised control trial comparing selexipag with and without background therapy, to placebo with and without background therapy in patients with WHO FC I-IV PAH. The submission presented a trial-based cost-effectiveness analysis, in which the incremental effectiveness was measured in terms of the reduction in the number of first morbidity or mortality (MM) events per person year over the duration of the trial, i.e. the ICER was the incremental cost per unit reduction in the number of first MM events per person-year.

The PBAC considered that the claim of superior effectiveness over placebo was reasonable and noted that the beneficial effect of selexipag over placebo was due to both a difference in disease progression and a lower rate of hospitalisation for worsening of PAH. However, there was no evidence that selexipag had a statistically significant effect on overall survival. The PBAC agreed with the submission that selexipag is inferior in terms of comparative safety in comparison with placebo. The PBAC considered that the appropriate place in therapy for selexipag was likely to be third line (dual and triple therapy), after patients have tried ERAs and PDE-5 inhibitors as monotherapy and in combination.

The PBAC rejected the listing of selexipag as it considered that the magnitude of clinical benefit was unclear and the estimate of cost-effectiveness difficult to interpret. It considered the ICER presented in the submission as high, especially in the context of an outcome of unclear clinical importance.

The March 2017 resubmission for selexipag[[5]](#endnote-5) requested PBS listing as third line treatment in combination with an ERA and PDE-5 inhibitor and second line in patients who are intolerant or contra-indicated to either ERAs or PDE-5 inhibitors. The resubmission presented a reanalysis of the GRIPHON trial results: an alternative composite outcome measure analysis, including time to first event for individual morbidity components of the composite outcome. It also reported on overall survival at the end of the study.

The PBAC remained of the view that selexipag was likely to be superior to placebo in terms of comparative effectiveness, but that the magnitude and clinical relevance of any benefit remained unclear. PBAC accepted the claim that selexipag was of inferior safety compared to placebo. The PBAC considered that it would be preferable to not specify the line of use in any listing other than as add-on therapy.

The PBAC did not recommend the listing of selexipag as the ICERs presented were difficult to interpret and were likely to be too high to support the cost-effectiveness of selexipag in the requested listing, even though the trial results were re-analysed. The PBAC considered that the most likely way to achieve a more acceptable ICER would be with a reduced proposed price as it is unlikely that new clinical data would be forthcoming.

Due to patent expiry, several PAH medicines are no longer PBS listed at their original cost-effective price and currently placed in the PBS Formulary 2. The price of these medicines is likely to continue to fall in the foreseeable future due to price disclosure and brand competition. These medicines include: bosentan (ERA); sildenafil (PDE-5 inhibitors); and epoprostenol (prostanoid). For combinations of these medicines, where there is data to support superior efficacy and non-inferior safety compared to monotherapy, cost-effectiveness could be considered acceptable where to total cost of treatment is no more than the original cost-effective price for the monotherapy.

# References

1. https://www.nice.org.uk/guidance/gid-tag382/documents/overview2 [↑](#endnote-ref-1)
2. Y-F Chen, S Jowett, P Barton eta al Clinical and cost-effectiveness of epoprostenol, iloprost, bosentan, sitaxentan and sildenafil for pulmonary arterial hypertension within their licensed indications: a systematic review and economic evaluation (2009) <https://www.ncbi.nlm.nih.gov/books/NBK56808/> [↑](#endnote-ref-2)
3. Canadian Agency for Drugs and Technologies in Health: CADTH Therapeutic Review Report: Drugs for Pulmonary Arterial Hypertension: Comparative Efficacy, Safety and Cost-Effectiveness – Recommendations Report March 2015 [↑](#endnote-ref-3)
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5. Selexipag: Tablet 200 mcg, Tablet 200 mcg, Tablet 400 mcg, Tablet 600 mcg, Tablet 800 mcg, Tablet 1000 mcg, Tablet 1200 mcg, Tablet 1400 mcg, Tablet 1600 mcg; Uptravi® Public Summary Document (PSD) March 2017 PBAC Meeting. [accessed 20 April 2018] http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2017-03/selexipag-psd-march-2017 [↑](#endnote-ref-5)