

CATAG submission:

Public Consultation on the Post-market Review of Pulmonary Arterial Hypertension (PAH) Medicines

April 2017

The Council of Australian Therapeutic Advisory Groups (CATAG) is an authoritative, expert, consensus-based collaboration of representatives from all Australian State and Territory Therapeutic Advisory Groups or their jurisdictional committee equivalents.

CATAG aims to standardise and improve medicines use primarily (but not exclusively) in the hospital sector across Australia through information sharing, advice and advocacy activities.

Contact for further information:
Jane Donnelly, National Coordinator
The Council of Australian Therapeutic Advisory Groups
Email: catag@stvincents.com.au

INTRODUCTION

The Council of Australian Therapeutic Advisory Groups (CATAG) believes it is timely to review the national utilisation of pulmonary arterial hypertension (PAH) medicines and welcomes the opportunity to provide a national hospital and health network perspective on formulary listings to assist in the utilisation analysis.

The Terms of Reference for the review include:

1. Review recent clinical guidelines for the management of PAH and compare this to the PBS restrictions and Therapeutic Goods Administration (TGA) indications for the use of PAH medicines.
2. Review the utilisation of PAH medicines in Australia, including sources of data that can provide additional information on clinical use that is not available from PBS data.
3. Review the clinical outcomes that are most important or clinically relevant to patients with PAH, and the extent to which these outcomes are included in the evidence previously considered by PBAC.
4. Collate and evaluate evidence on the comparative effectiveness of PAH medicines, including combination use and use in the WHO functional class II patient populations.
5. 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.

These considerations form the basis of CATAG's response to the consultation, however the focus of this submission is to provide a source of medicines utilisation data, which is not available from PBS data.

METHODS

CATAG determined the most appropriate pathway to obtain the requested information was to survey hospitals through its members' networks. A survey was conducted electronically utilizing Survey Monkey™ from 13th to 24th March 2017. The survey template is attached in Appendix 1. Analysis and reporting was undertaken by the CATAG Coordinator, ethics approval was not obtained and the data are therefore to be treated as confidential. Throughout the report the number of responses varies for each question; respondents were able to skip questions if they wished.

RESULTS

Jurisdictional, health district and institutional representation

Participation in the survey was requested from Drug and Therapeutics Committees (DTCs) across Australia. Responses were received from all jurisdictions in Australia.

Queensland, South Australia, Tasmania and Northern Territory operate state-wide formularies although hospitals within these jurisdictions also have DTCs to locally implement formulary decisions and manage medicine requests for individual patients. Some survey responses from SA and Qld did not acknowledge the operation of a state-wide formulary; this is most likely due to their local activity managing individual patient requests for PAH medicines. (Where appropriate e.g. discussion of state-wide formularies, these responses have been combined to represent the relevant jurisdiction, as these answers did not vary within the jurisdiction). Thirteen DTCs responded from these jurisdictions. Victoria, New South Wales and Western Australia have district and/or institution-based DTCs that manage formulary and individual patient requests. Sixteen DTCs responded from these jurisdictions.

Table 1 indicates the type of Drug and Therapeutics Committee (DTC) that responded to the survey. The states are disproportionately represented, compared to population size in the survey results. Fourteen percent of responses were from NSW (4/29) and 31% of responses from Queensland (9/29). According to the ABS 2016, approximately 32% of Australians reside in NSW and 20% in Queensland. However it should also be noted that PAH is a rare condition and that there are hospitals that are specialty centres for its management and referral pathways and the funding framework for PAH medicines may differ within jurisdictions. This is evident in that there were few responses from rural hospitals or districts; x% responses were from metropolitan and regional areas.

Table 1: Jurisdictional, district and institutional Drug and Therapeutics Committees representation, n=29

Drug and Therapeutics Committee description	Jurisdiction	Response Count
State-wide	Qld, NT, Tas	3 Qld, 1 NT, 1 Tas
Metropolitan health district/network	Vic, SA	1 Vic, 2 SA
Regional health district/network	WA, NSW, Qld	1 WA, 1 NSW, 1 Qld
Rural health district/network		0
>250 bed metropolitan hospital	ACT, WA, Qld, NSW, Vic	1 ACT, 2 WA, 5 Qld, 2 NSW, 1 Vic,
100-250 bed metropolitan hospital		0
<100 bed metropolitan hospital	Vic	1 Vic
>150 bed regional/rural hospital	NSW	1 NSW
51-150 bed regional/rural hospital	WA, Vic	1 WA, 2 Vic
<50 bed regional/rural hospital		0
Specialist women's hospital	Vic	1 Vic
Specialist children's hospital	WA	1 WA
Specialist psychiatric hospital		0
Specialist rehabilitation hospital		0

National overview of formulary listings – March 2017

Collated formulary listings are displayed in Figure 1. Three PAH medicines, macitentan, ambrisentan and iloprost, were listed on formularies for PBS-approved indications. Sildenafil was the medicine most frequently listed for non-PBS indications (n=7). To a lesser extent, epoprostenol (n=3) and tadalafil (n=1) were also listed for non-PBS indications. Respondents were asked to identify where formulary listings differed from the PBS and to provide a rationale for non-listing. Five out of 10 respondents noted the differentiation of the sildenafil formulary listing from the PBS listing was to allow for combination therapy (i.e. treatment with more than one PAH agent). Hospitals/districts that did not list PAH medicines on formulary or did not list the medicine on the formulary for a specific indication require prescribers to make individual patient use (IPU) requests to the DTC for supply. A question regarding hospital/district formulary listing of bosentan in Victoria, NSW and WA were not obtained in this survey.

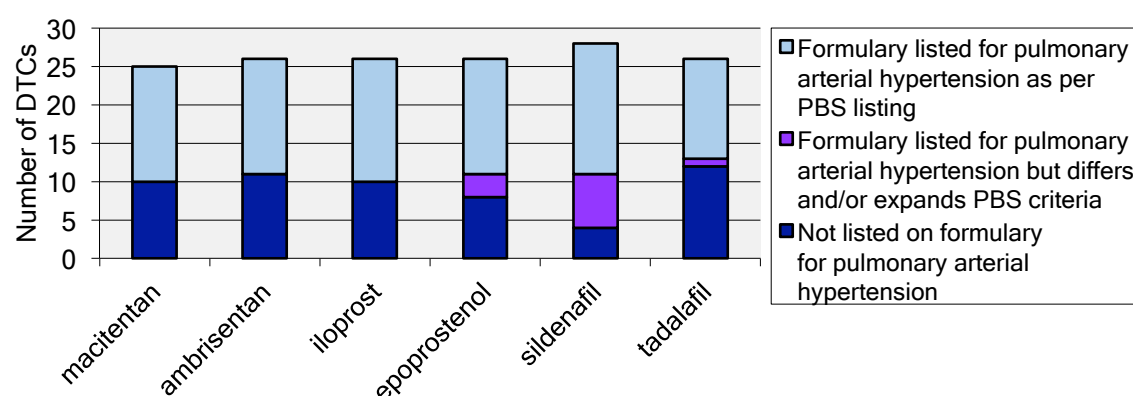


Figure 1: Formulary listings of medicines used for the treatment of pulmonary arterial hypertension, n = 28

Formulary listings by jurisdiction – State-wide formularies

A breakdown of formulary listings according to whether it is a state-managed or district/institution DTC is shown in Table 2 and Figure 2. State-wide DTCs have taken varying approaches to PAH medicine formulary listing. For example, in Queensland, all PAH medicines are listed on formulary as per the PBS listings and there is no differentiation from the PBS. Tasmania has taken a similar approach although indications for PDE5 antagonists are expanded. In contrast, in South Australia, only one medicine from each pharmacological class is formulary listed as per PBS indications (e.g. bosentan from the endothelin antagonist class and epoprostenol from the prostacyclin class). Sildenafil is the only PDE5 antagonist, however its listing differs from the PBS listing, it can be used for the management of PAH as part of combination therapy. The South Australian formulary determinations were made in 2015; at the time the 3 endothelin antagonists (ambrisentan, bosentan and macitentan) were considered therapeutic alternatives, with more evidence to support bosentan and also more usage within SA Health. Iloprost was not listed on the SA statewide formulary, as it was considered more appropriate to utilize the individual patient usage (IPU) process, due to the medicine's highly specialized use and anticipated small patient numbers.

Table 2: State-wide formulary listings of PAH medicines, n=4

JURISDICTION	MACITENTAN	AMBRISENTAN	BOSENTAN	ILOPROST	EPOPROSTENOL	SILDENAFIL	TADALAFIL
QUEENSLAND	✓	✓	✓	✓	✓	✓	✓
SOUTH AUSTRALIA			✓		✓	p	
TASMANIA	✓	✓	✓	✓	✓	p	p
NORTHERN TERRITORY			✓	✓	✓	✓	

p Listed on formulary, listing differs from the PBS

✓ Listed on formulary as per PBS listing

Formulary listings by jurisdiction – Hospital and district/network formularies

As displayed in Figure 2, there is diversity in the decisions by district and hospital DTCs regarding formulary listings of PAH medicines. Consistent with state-wide DTC formulary listings, tadalafil is the least likely PAH medicine to be listed on a hospital formulary for the treatment of PAH. A quarter of DTCs expanded the indications in their formulary listings of sildenafil for which sildenafil could be used.

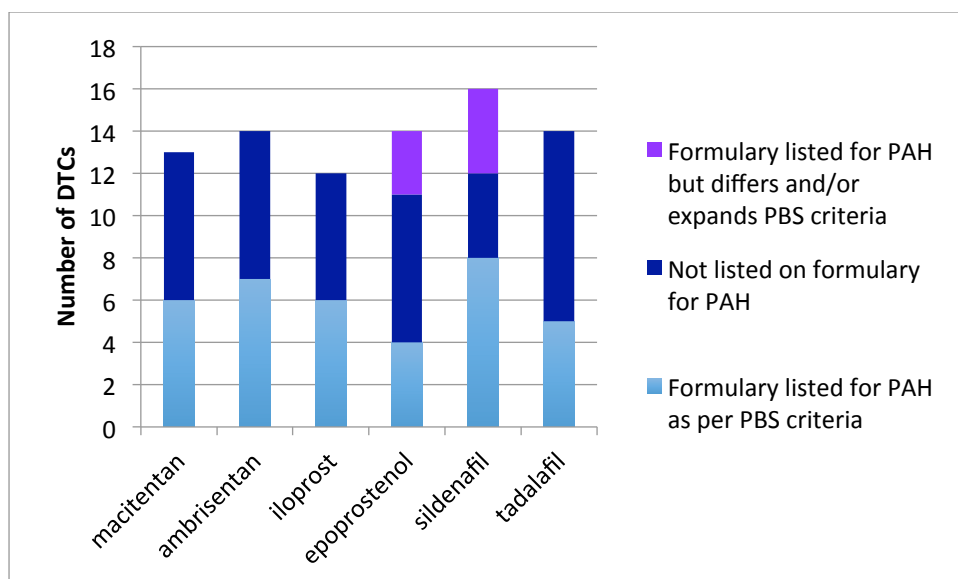


Figure 2: Formulary listings for PAH medicines in jurisdictions without state-wide formularies (NSW, Victoria, ACT and WA)

Formulary listings allowing combination therapy

Current treatment guidelines recommend combination therapy for patients who exhibit an inadequate clinical response or who deteriorate on monotherapy¹. Utilising combination therapy targets distinct PAH signalling pathways, therefore potentially acting synergistically to treat PAH.

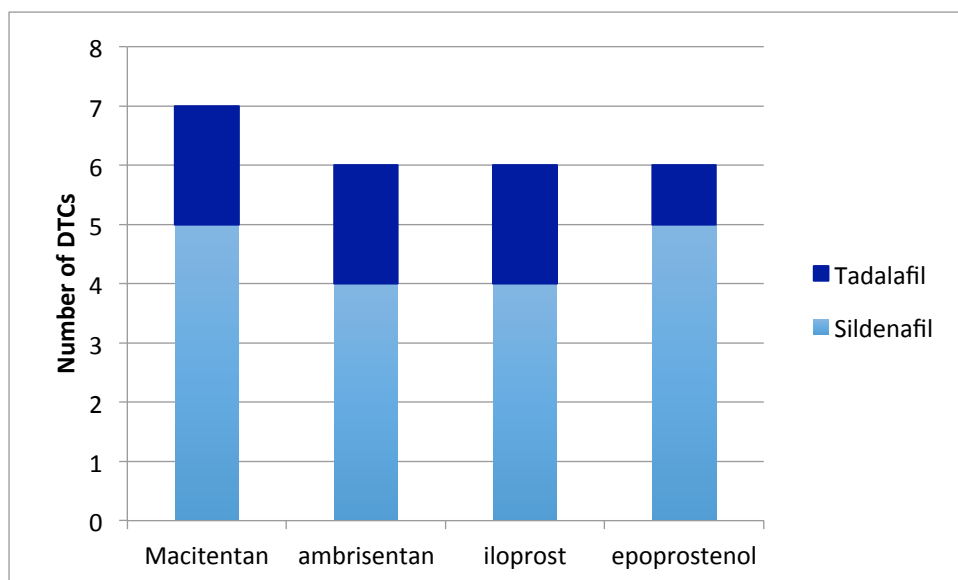


Figure 3: Formulary listings approving combination therapy to treat PAH

Seven DTCs, 3 with state-wide formularies and 4 with hospital/district formularies (of the hospital/district formularies, 3 of these were metropolitan hospitals and 1 was a specialist women's

¹ Galiè N, Corris PA, Frost A, et al. Updated treatment algorithm of pulmonary arterial hypertension. J Am Coll Cardiol. 2013;62(25, suppl):D60-D72.

² Individual patient use is defined as the use of a medicine by an individual patient outside the hospital formulary

hospital) reported their formulary listings allowed combination therapy. South Australia and Tasmania have approved combination therapy in their state-wide formularies. South Australia has approved combination therapy with bosentan and sildenafil. Tasmania has approved sildenafil and tadalafil in combination with the endothelin antagonists. Other jurisdictions where combination therapy has been approved include hospitals in Western Australia and Victoria.

Respondents were asked to provide a reason when combination therapy was not approved. Twenty-two responses were received. The majority of respondents (59%) stated that formulary listing of combination PAH therapy was not approved due to the PBS listing limitations regarding combination therapy. In these situations, individual patient use (IPU)² approvals by the DTC are required in order to access combination therapy.

Individual patient use requests for PAH medicines

In order to determine whether institutions receive requests to fund therapy in addition to formulary listings, respondents were asked if their institution had received IPU requests for macitentan, ambrisentan, bosentan, iloprost, epoprostenol, sildenafil and tadalafil to treat PAH between December 2014 and December 2016. More than 70% (15/21) stated they had received IPU applications. The six DTCs who stated they did not receive IPU requests, 4 were from Victoria, 1 from Qld and 1 from Tasmania. The four DTCs from Victoria represented a specialist womens hospital, 51-150 bed regional/rural hospital and a <100 be metropolitan hospital.

DTCs were asked whether they had received IPU requests for specific PAH medicines (Figure 4). Almost all DTCs (12/15) had received IPU requests to supply and fund sildenafil. [These IPU requests were required because either sildenafil was not listed on formulary (4 DTCs) or the patient's indication did not align with the formulary listing, (as per PBS criteria)]. In contrast, far fewer DTCs received IPU applications for other PAH medicines. Figure 5 displays the volume of IPU requests for each PAH medicine. Again, there were a significantly greater number of IPU requests for sildenafil compared to the other PAH medicines. The IPU requests for sildenafil (in preference to other PAH medicines) as part of a combination therapy regimen was likely influenced by the patent expiration of sildenafil (Viagra®) in May 2014 and consequent significant reduction in sildenafil cost. For patients utilising combination therapy, institutions may have been willing to fund the cheaper medicine (sildenafil) with access to the more expensive medicine enabled through the PBS.

² Individual patient use is defined as the use of a medicine by an individual patient outside the hospital formulary regulations. Approval for IPU specific medicines is required when a therapeutic need exists for a medicine, which would not otherwise be available on the institution's formulary *Council of Australian Therapeutic Advisory Groups. Achieving effective medicines governance: Guiding Principles for the roles and responsibilities of Drug and Therapeutics Committees in Australian public hospitals. 2013*

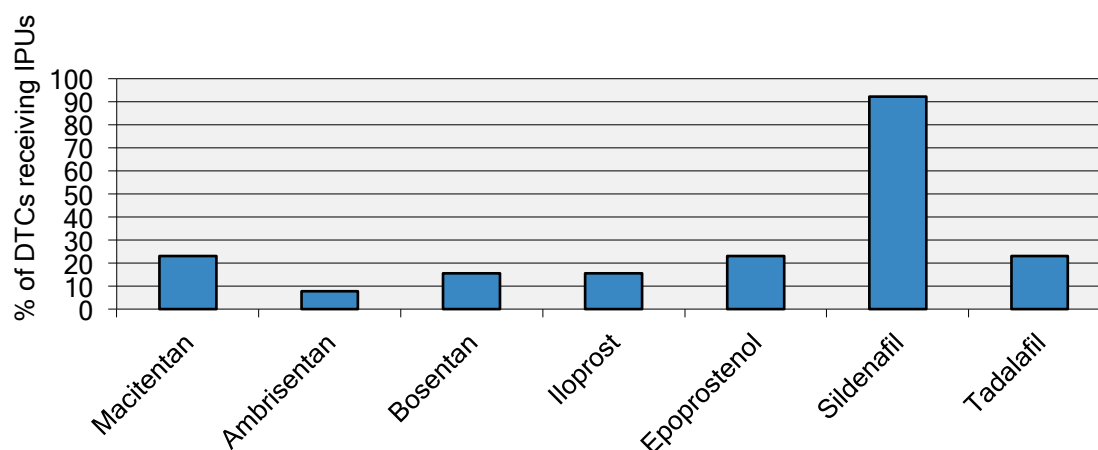


Figure 4: Percentage of DTCs receiving individual patient use applications for PAH medicines, December 2014 to December 2016, n=13

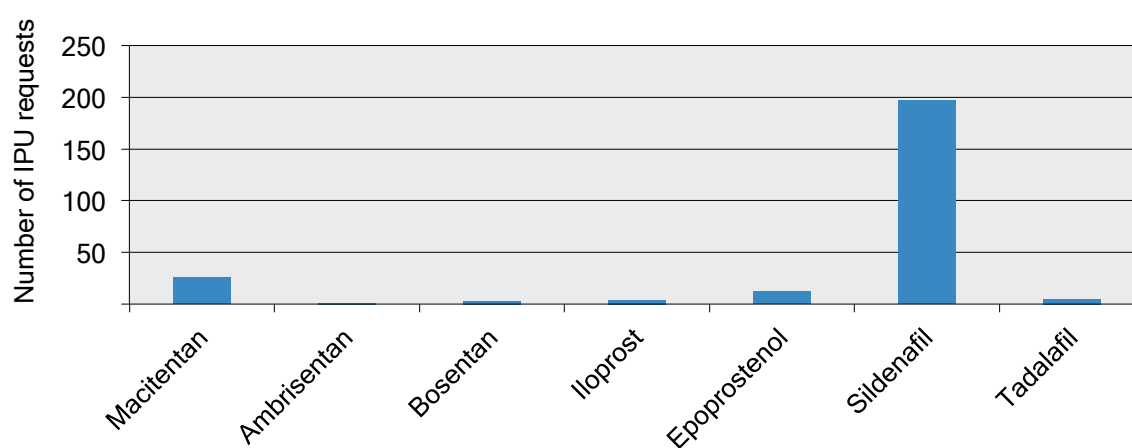


Figure 5: Number of IPU requests received by 15 DTCs for specific PAH medicines, December 2014 to December 2016

Decisions to approve or not approve IPU requests

Respondents were asked to indicate whether the IPU requests were approved for each PAH medicine. This question was designed to determine whether institutions were funding PAH medicines when patients couldn't access these medicines via the PBS. Twenty DTCs reported that all IPU requests for macitentan, iloprost, epoprostenol and sildenafil were approved to treat PAH.

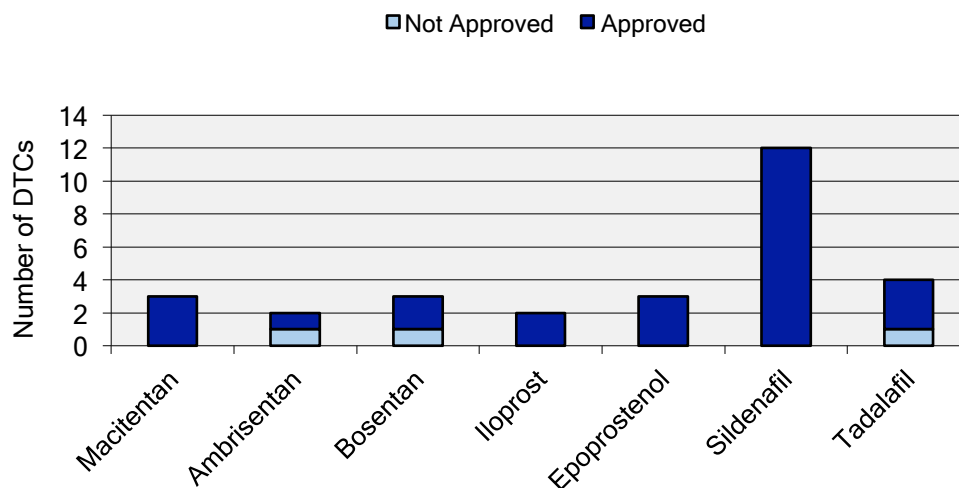


Figure 6: Approval and non approval of IPU requests for specific PAH medicines

There were 197 IPU requests for sildenafil (Figure 5) but only 12 approvals (Figure 6). This is mainly due to blanket approvals determined by a number of institutions for combination therapy. This is where one determination or approval is made for a number or a group of patients.

Reasons for approval and non-approval for each medicine are described below:

Macitentan: Three DTCs approved macitentan for IPU a) in the inpatient setting, b) as continuation of therapy and c) for use in combination therapy.

Ambrisentan: One DTC approved ambrisentan use when a patient did not tolerate sildenafil. One respondent stated ambrisentan was not approved for use due to macitentan being superior and ambrisentan not being indicated on the PBS for the proposed indication.

Bosentan Two DTCs approved bosentan for use in combination therapy and where the medicine was not available on formulary. One respondent stated bosentan was not approved for use due to macitentan being superior.

Iloprost: Two DTCs approved iloprost for use in combination with other PAH medicines when a patient was not significantly responsive to treatment with sildenafil and macitentan.

Epoprostenol was approved for IPU in the following circumstances (1 DTC approved epoprostenol for two indications):

- Severe PAH from porto-pulmonary syndrome not responding to PD5 inhibitor therapy. Unable to be included onto liver transplant list as pulmonary hypertension too high and requiring frequent inpatient admissions. Deemed to be cost effective to prevent inpatient admissions
- Combination therapy with another PAH agent

- Debilitating symptoms despite treatment with ambrisentan, sildenafil and bosentan
- One-off use in a perioperative patient due to underlying PAH

Sildenafil was approved for IPU in the following circumstances:

- Use in combination with another PAH agent (50% of responses N=12)
- Patient was unable to fund the cost
- Continuation of therapy initiated at a tertiary referral centre
- Failure of current therapy

Tadalafil was approved by 3 DTCs for compassionate use in combination with another PAH agent and when a patient experienced significant gastrointestinal upset with the use of sildenafil. Tadalafil was not approved for IPU by 1 DTC, as sildenafil was determined by that DTC to be the preferred agent.

Estimated cost of IPU/IPA PAH medicines

Respondents were asked to estimate the costs of providing PAH medicines in their institution through the IPU processes (i.e. provision outside PBS arrangements). The cost estimates only related to providing the medicine and did not encompass the clinical or administrative costs associated with supply of the PAH medicines. Fourteen responses were received: four DTCs stated the supply of IPU-approved medicines ranged between \$100 and \$2,900 over a two-year period. Three institutional DTCs responded the costs were estimated to range between \$3,000 and \$4,900 over a two-year period. Three institutions responded the costs were estimated between \$5,000 and \$15,000 over a two-year period. Two institutions responded the costs were between \$40,000 and \$100,000 over a two-year period and one institution estimated the cost between \$100,000 and \$200,000 over a two-year period. Those with higher costs are tertiary referral centres with a specific focus on PAH.

PAH Medicine Access Programs

Sponsors may provide cost-free or subsidised mechanisms for accessing medicines outside the PBS and hospital funding mechanisms (e.g. via IPU requests). These Medicines Access Programs (MAPs) facilitate deferred cost, cost-free or subsidised medicines supply to hospital patients (usually outpatients) before the implementation of relevant funding arrangements. MAPs include, but are not limited to, compassionate use programs, expanded access programs, product familiarisation programs and cost share programs³.

³ Council of Australian Therapeutic Advisory Groups. Managing Medicines Access Programs. Guiding principles for the governance of Medicines Access Programs in Australian hospitals. CATAG, 2015.

CATAG specifically investigated the extent to which MAPs related to PAH medicines are operating in institutions in order to highlight the mechanisms which clinicians and patients utilise alternative pathways to access PAH medicines. Thirty-two percent of DTC respondents (6/19) provided PAH medicines through a MAP during December 2014 and December 2016.

It is notable that some access programs are operating through community pharmacies and therefore district/hospital Drug and Therapeutics Committees are not aware of their operation or that patients from their institution are accessing medicines through this mechanism. This may be a reason for the low number of DTC responses, and the seemingly small number of patients utilising these programs as reflected in the survey responses.

Prior to the survey, CATAG understood there were two formalised pharmaceutical company-initiated PAH MAPs in operation, therefore these were specifically included in the survey question:

1. GSK MedACCESS - tadalafil with PBS Volibris (ambrisentan) 5/9 respondents were operating this MAP
2. Actelion PACT (Patient access to combination therapy) - PBS macitentan and PDE5i medication (either sildenafil or tadalafil) 4/9 respondents were operating this MAP

Respondents were asked to identify the MAPs and their category (including compassionate access, product familiarisation, expanded access and cost share programs) that were operating in their institutions between December 2014 and December 2016. Further information regarding these MAPs is explored in the discussion. Eight institutions supported compassionate access programs, two of these specific to sildenafil and another to macitentan. Other types of programs such as product familiarisation programs, expanded access and cost share programs were not in operation at the institutions that responded to the survey.

Respondents were asked the number of patients enrolled in each of the programs

1. GSK MedACCESS - tadalafil with PBS Volibris (ambrisentan):
Three DTC respondents noted 1-7 patients were utilising tadalafil through this program
2. Actelion PACT (Patient access to combination therapy) - PBS macitentan and PDE5i medication (either sildenafil or tadalafil)
One DTC respondent noted 8 patients were utilising either sildenafil or tadalafil through this program
3. Compassionate access
Four DTC respondents noted 3-5 patients were utilising PAH therapy through compassionate access programs at their institution. One institution, a metropolitan/health district network DTC noted 70 patients were utilising PAH therapy through a compassionate access program and were concerned that a pharmaceutical company could withdraw their compassionate access program leaving patients vulnerable and without therapy.

Concerns regarding PAH medicines management in hospital or the community

Through various forums and stakeholder discussions, CATAG is aware of concerns regarding PAH medicines access in both hospital and community settings. Respondents were able to respond about concerns using a free text field; responses were thematically analysed. The following themes were

identified: inequity of access, PBS restrictions, hospital funding of medicines and incentivised supply arrangements.

Inequity of access to PAH medicines

A number of respondents expressed concerns regarding the inequity of access to PAH medicines. There is inequity of access to PAH medicines depending on the institution which patients are referred to for treatment. Varying decision-making regarding whether to fund combination therapy by DTCs may lead to inequitable access. One respondent noted, *“PAH patients are not receiving fair and adequate access to evidence-based therapy that is based on international guidelines.”* The survey has provided evidence of varied decision-making.

Furthermore, not all designated PAH centers listed on the Department of Human Services Website (<https://www.humanservices.gov.au/health-professionals/enablers/pulmonary-arterial-hypertension-designated-centres>) are engaged with companies operating MAP programs leading to inequity of access to combination therapy. This may also lead to patients seeking treatment at certain centers. The survey demonstrated that some hospitals are carrying a significant financial and governance burden. Another concern regarding community- and hospital-based MAPs is that they could *“withdraw compassionate access leaving patients without required therapy.”* This exposes both the patient and the institution at which the patient is being treated to unnecessary financial burden should treatment be required to continue.

Current PBS restrictions

Respondents noted there is ongoing concern with regard to the current PBS restrictions, which do not allow combination therapy. Respondents noted this is inconsistent with current guideline recommendations.⁴ The current PAH treatment algorithm, as updated following the 5th World Symposium on Pulmonary Hypertension, indicates that the addition of a second treatment in addition to background therapy may be considered when an inadequate clinical response or deterioration is observed with monotherapy in patients in World Health Organization (WHO) functional class III/IV.⁵ The current PBS restrictions do not allow for sequential or initial combination therapy in any PAH WHO functional class.

Hospital funding of medicines

A number of respondents noted the hospital or institution funds PAH treatment, when patients have not achieved an adequate clinical response to monotherapy. Hospital-funding of medicines creates a number of complexities for patients. Patients need to access the medicine from the designated institution which is funding the medicine. Patients who are treated at an institution which is a significant distance from their residence would need to attend the institution to pick up their medicine. The intervals at which review appointments and medicine dispensing requirements occur may differ. This creates a significant burden for patients physically and financially.

⁴ Galiè N, Humbert M, Vachiery J-L, et al. 2015 ESC/ERS Guidelines for the diagnosis of pulmonary hypertension: The Joint Task force for the Diagnosis and treatment of pulmonary Hypertension of the European Society of Cardiology (ESC) and European Respiratory Society (ERS) <https://academic.oup.com/eurheartj/article/37/1/67/2887599/2015-ESC-ERS-Guidelines-for-the-diagnosis-and#54534810>

⁵ Galiè N, Corris PA, Frost A, et al. Updated treatment algorithm of pulmonary arterial hypertension. *J Am Coll Cardiol* 2013; 62 Suppl. 25:D60–D72

Incentivised supply arrangements

A concerning feature of one PAH MAP currently operating is the engagement of a group of community pharmacies to be the sole suppliers of a MAP medicine. These pharmacies have been contracted by the pharmaceutical company to supply specific medicines and receive financial incentives to operate. It is unclear whether these MAPs are governed by a DTC. Although community pharmacy-based programs have the potential to be closer to the patient's residence, the complexity of PAH and the knowledge and skill base of the community pharmacist to assist with this uncommon condition may not be adequate. Appropriate clinical governance of such programs to ensure quality use of medicines is critical.

Addendum – Riociguat

CATAG was advised in April 2017, of an additional medicine to be included in the PAH PBS review, riociguat. CATAG requested information from all jurisdictions through its member networks via email. Three jurisdictions responded South Australia, Queensland and Victoria. Both Queensland and South Australia operate statewide formularies, four health services responded from Victoria. The responses from all jurisdictions were similar. Riociguat is not formulary listed in any of the responding three jurisdictions. There have been no individual patient usage (IPU) requests. There is a medication access program operating, which identified as a product familiarisation program (PPF) in a single local health network.

DISCUSSION

The current PBS listings for PAH medicines do not allow for combination therapy at any time during disease progression. There are currently a number of mechanisms by which clinicians and patients access PAH medicines in addition to using a PBS PAH medicine: medication access programs, hospital funding and private funding. The mechanisms by which institutions are accessing medicines for PAH sufferers are increasingly burdensome and result in significant indirect costs to patients. Institutions are investing significant resources to review IPU applications, and provide clinical governance for MAPs and ongoing administration.

There is considerable variation in decision-making by DTCs, evidenced through the differences in formulary listings. SA's and Tasmania's state-wide formularies allow combination therapy, however Queensland's does not. Despite state-wide formulary listings, all jurisdictions are significantly burdened by IPU review, MAP review and governance. Although DTCs generally operate independently of each other, there are informal decision sharing networks such as CATAG and jurisdictional TAGs. Factors related to the variation in DTC decision making may include variations in DTC composition, expertise and skill, varying ability to undertake pharmaco-economic evaluation and financial resourcing. The variation in decisions can also lead to concerns regarding equity of access to medicines.

There are two PAH MAP programs currently offered by pharmaceutical companies. These programs are generally operating outside formal clinical governance. Although specifically written for public hospitals medicines management processes, CATAG's Guiding Principles for the governance of Medicines Access Programs in Australian hospitals has, key concepts applicable to all care settings. It is recommended approval of a MAP be delegated to, and obtained from, a committee with the required authority and expertise prior to the enrolment of any patients in the MAP. The process for a MAP being reviewed by an appropriate committee provides transparency, propriety and avoids conflicts of interest. The review process also enables a risk assessment with subsequent implementation of risk mitigation strategies, as appropriate. These processes do not occur when a MAP is initiated in the community or outside of appropriate clinical governance structures, exposing patients to potential clinical and financial harm. MAPs may provide benefits for patients, clinicians and pharmaceutical companies; however these benefits need to be clearly discussed with patients and clinicians in order that informed decisions are made regarding the utilisation of medicines through such programs.

The survey responses highlight the complexities patients and clinicians are required to navigate in order to receive and provide treatment. The disease is complex and progressive, and clinicians require specialist expertise to diagnose and manage patients. In 2015, the Pulmonary Hypertension Society of Australia and New Zealand reported there were significant differences in mortality between centres ⁶. There are now a large number of PAH designated centres, possibly with varied expertise. This creates two identifiable issues with regard to medicines management: potential inequity of access and variation in clinical expertise leading to a variation in treatment. Less experienced clinicians or those with fewer patients potentially may practice differently to more experienced clinicians.

LIMITATIONS

As CATAG sent the survey to its member jurisdictions to disseminate through their networks to individual public hospitals and health networks, a response rate is unable to be determined. The short turn-around time from survey release to closure would also have affected sample size significantly. All jurisdictions were represented in the survey, the only demographic collected was the type of DTC which was operating. Bosentan was inadvertently omitted from the first three survey questions; therefore the listing of bosentan for those institutions who do not utilise a state-wide formulary was unable to be determined.

6Pulmonary Hypertension Society of Australian and New Zealand, Australia and New Zealand PHT registry, 3rd annual report 2015
<http://www.phsanz.com.au/Portals/0/downloads/PHSANZ%202015%20Registry%20report%20Oct%202015%20final.pdf>