PAH Review Secretariat

Ref: Post-Market Review of Pulmonary Arterial Hypertension (PAH) Medicines - Actelion Response

Draft Terms of Reference

Actelion welcomes the review of recent ERS/ESC guidelines for the management of PAH and is appreciative of being able to make a submission.

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.**

   Australia reimburses treatment of PAH in a manner that is different from most other Western nations. The result of this is that some PAH patients have a vastly inferior access to consensus best practice treatment than they would have elsewhere.

   Since the different aetiologies of PAH in Group 1 share similar pathological findings and hemodynamic characteristics, disease management recommendations do not differentiate between them and PAH medicines in other countries are generally reimbursed for the complete WHO Group 1 PAH. In Australia the cause of PAH determines if a patient can receive treatment or not, this distinction in funding by the cause of PAH is not seen to be meaningful. Actelion is not arguing against the evidence-based nature of Australia's assessment or its cost effectiveness guidelines. However, we would make the point that as PAH is a rare disease, conducting clinical trials in very selected sub-populations is neither feasible nor realistic. Thus, the current PBS restrictions would seem to arbitrarily discriminate against these unlucky patients which make up less than 10% of the existing patient pool.

   The most recent ESC/ERS guidelines (2015) advocate a risk-based approach to the treatment of PAH with the overall assessment of the patient's risk profile (based on e.g. WHO FC II, symptom progression, absolute 6-minute walk distance (6MWD) at baseline) driving therapeutic decisions with regard to which drugs to prescribe and how and when to combine them. The overall treatment goal in patients with PAH is two-fold: First, to achieve a low-risk status for the patient and secondly, to improve the patient's function, health-related quality of life and symptoms.

   For patients who do not meet these treatment goals, the guidelines mandate the utilisation of combination therapy for the management of PAH supported by the growing evidence from event-driven, long-term outcomes studies. However in Australia, there is inequitable access to combination therapy in PAH due to the fact that PBS funding is not permitted for more than one agent at any given time.

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Actelion believes that PAH patients in Australia would benefit if access to PAH medicines was more aligned with international treatment guidelines as they represent the most recent available evidence and experience. We are convinced that any major deviation from these guidelines will translate into inferior patient outcomes for Australians being treated for PAH.

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.

The 2015 DUSC report for PAH medicines provide a very good overview on the use of subsidised therapies.

Actelion agrees with the findings of the 2015 DUSC report for PAH medicines that the disease is managed mainly by a dozen expert centres and that the modest growth rate is driven by the availability of innovative PAH treatments which have been shown to have an effect on patients' long-term outcomes.

However, the DUSC report fails to capture therapies that are funded via different routes such as hospital funds, patient self-pay or compassionate access by pharmaceutical companies.

The Australian PAH registry which is run by the Pulmonary Hypertension Society Australia and New Zealand (PHSANZ) contains extensive data on Australian patients with PAH and their treatments irrespective of source of funding. Actelion is convinced that it is the best source of real-world evidence for PAH in Australia and it should be utilised to gain Australia-specific insights.

The Australian PAH registry will also reveal that patients' access to late-stage therapy such as i.v. epoprostenol is very limited due to substantial infrastructure requirements associated with a particular therapy. Implementing a formal link between all treatment centres and their corresponding major centre would help to reduce the level of inequitable access that currently exists across Australia.

As one of the sponsors of the disease registry, Actelion is committed to ensuring that appropriate analyses of the registry data are available to help inform the review of the utilisation of PAH medicines in Australia.

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.

PAH is a rare, chronic disease which, if left untreated, progresses rapidly, leading to right heart failure and death. Although survival rates have improved since the launch of PAH-specific therapies, prognosis remains very poor (particularly for patients with more advanced disease) and is worse than that associated with several forms of cancer.

Historic clinical studies in PAH focused on changes in exercise capacity over the course of 12 to 24 weeks, and drugs like bosentan and sildenafil have been approved and funded based on this evidence. In recent years, the knowledge about PAH has advanced significantly.

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Among others, it has been demonstrated and acknowledged that, although the absolute 6MWD value is predictive of mortality, changes in 6MWD are not associated with long-term outcomes such as morbidity and mortality. Consequently, international guidelines as well as regulatory agencies (EMA) nowadays mandate the assessment of the impact of new PAH therapies on disease progression/morbidity and mortality.

The use of a composite primary endpoint that measures morbidity and mortality was recommended at the 4th World Symposium on Pulmonary Hypertension, held in Dana Point in 2008, and subsequently confirmed at the 5th WSPH, held in Nice in 2013. The importance of patient and clinically relevant long-term outcomes, including among others hospitalizations and the application of invasive therapies as well as disease progression, has therefore been acknowledged, and it is the global consensus view that these long-term outcomes have to be the basis for decision-making.

Qualitative research in PAH patients support the relevance of M/M endpoints, having demonstrated that patients worry about how their disease progresses, they want to stay out of hospital; they want to avoid more invasive therapies for as long as possible, and they fear that they will die prematurely due to PAH. Furthermore, patients with PAH experience a debilitating symptom burden and severe impairment of health-related quality of life significantly impacting their daily lives and the lives of their carers.

Evidence on long-term outcomes is available from the more recent, event-driven studies in PAH, ie, COMPASS-II, SERAPHIN, GRIPHON, and AMBITION. For PAH medicines currently funded by the PBS, only the submission for macitentan to the PBAC included long-term outcomes and the PBAC agreed that these were more clinically meaningful than the short-term outcomes used in historic studies in PAH.

4. Collate and evaluate evidence on the comparative effectiveness of PAH medicines, including combination use and use in the WHO functional class ll patient populations.

Actelion welcomes the assessment of PAH medicines based on comparative effectiveness including combination use and use in WHO functional class ll patients. As described above (see 1), combination therapy has become a cornerstone in PAH therapy for patients not meeting their treatment targets. Clinical evidence has shown that treating PAH earlier such as WHO functional class II leads to better long-term outcomes than treatment initiation at a later stage. Given that only 15 % of all diagnosed patients in Australia are in WHO functional class II, the financial impact of treating these patients would be limited.

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In order to be meaningful for clinicians and patients, such evaluation needs to be based on long-term outcomes, which are available from four studies in PAH (COMPASS-II, SERAPHIN, GRIPHON, AMBITION). However, the evaluation needs to account for the key differences in trial design, endpoint definition and patient populations in these studies and also the lack of head to head data.

Even though evidence on change in exercise capacity is available for all drugs approved in PAH, the clinical value of such information is very limited. As described above, change in exercise capacity is not predictive of long-term outcomes. Findings from the Australian PAH registry confirm this point: Patients receiving bosentan as first-line therapy compared to patients receiving sildenafil as first-line therapy showed a survival advantage even though the short-term studies for both products demonstrated similar effects in change of 6MWD.

Therefore, any comparative effectiveness of PAH medicines needs to be focused on long-term clinical outcomes as well as safety information in comparable patient populations using comparable endpoints. However, before doing so, the feasibility and meaningfulness of an indirect treatment comparison needs to be assessed carefully.

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.

Bosentan was shown to be a cost-effective therapy in PAH in Australia in 2004, at a price in excess of the current reimbursed price. Since then, all PAH medicines listed on the PBS have demonstrated their cost-effectiveness compared to bosentan.

The availability of generics for sildenafil (in 2014), bosentan (expected in 2017) and tadalafil (expected in 2017) is reducing the cost of treating PAH. While it may not be a criterion that the PBAC can consider in making funding decisions, Actelion believes that any increase in cost of therapy associated with the introduction of funding for combination therapy in suitable patients or access to treatment for patients in WHO FC II would be off-set by the savings accrued from the generic versions of these three agents. In addition, PBS funding of combination therapy and treatment of WHO FC II will lead to cost offsets in the mid to long-term due to delayed disease progression which will avoid costly hospitalisations and which will also allow patient to remain in the workplace for longer, all of which provide unrecognized but significant benefit to both the community and to government finances.

Furthermore, re-assessing the cost-effectiveness of PAH medicines currently funded in Australia would depend on the feasibility of comparing individual medicines or treatment strategies in terms of their effect on long-term outcomes in PAH as described above.

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