Response to Draft Terms of Reference PAH Post-market Review

16th May 2016

Introduction

GlaxoSmithKline (GSK) recognises the Government's responsibility to maintain a robust Pharmaceutical Benefits Scheme (PBS), and we further recognise that Post Market Reviews (PMRs) can play a role in ensuring the Quality Use of Medicines (QUM) accessed via the PBS.

GSK is committed to working with Government to ensure a robust process is followed for the Pulmonary Arterial Hypertension (PAH) PMR, as per the PMR framework. Furthermore, in line with the framework, GSK strongly recommends that the PMR include full information on the triggers for the review. This allows key stakeholders to provide relevant input into the Terms of Reference (ToR) and ensures uniformity of their understanding of the issues.

GSK remains concerned that there appears to be no mechanism for ensuring relevant sponsors are informed of an impending review prior to the draft ToR being announced. In triggering a therapy-wide review the Department should be particularly mindful of the implications for key stakeholders, including peak bodies and expert groups not typically monitoring the PBS and Pharmaceutical Benefits Advisory Committee (PBAC) processes, and take specific steps to ensure they are reasonably notified.

Finally, GSK welcomes constructive collaboration with the Department and the PBAC on this review to address any agreed genuine concerns, which are supported by data or medical professional advice. We are also committed to contributing to this review our technical knowledge and expertise on the important PAH medicines we supply through the PBS to Australian patients.

Scope

Draft Terms of Reference

Accepting the available information, GSK has provided a short summary of feedback for consideration.

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.***

   It would be useful to define which recent clinical guidelines will form the basis of this ToR. Whilst no local Australian clinical guidelines exist for PAH, there are two applicable international guidelines, specifically 'Updated treatment algorithm of pulmonary arterial hypertension' (Galie, ACC 2013), which presents the updated treatment algorithm as endorsed at the 5th World Symposia on Pulmonary Hypertension (PH), a meeting which is held every 5 years, and most recently the availability of 'Guidelines for the diagnosis and treatment of pulmonary hypertension' (Galie, ESC/ERS 2015). GSK considers the ESC/ERS 2015 guidelines to be the most relevant for the purposes of the PMR as they incorporate the latest evidence for combination therapy.

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.***

   In order to address this particular ToR, it may be beneficial to consider data sources available through the Pulmonary Hypertension Society of Australia & New Zealand (PHSANZ), a not for profit organisation with a mandate to advocate for a sustainable 'model of care' with equitable access to skilled clinicians that allows timely diagnosis, treatment and ongoing management for patients with PH in Australia and New Zealand. An early focus of the Society was to set up a National PH registry, which provides a platform for research and improves our understanding of PH. The registry offers comprehensive insights into the current demographics of the patient population and mortality based on aetiologies of PH and first treatment. The 3rd annual report (Oct 2015) is available via the following link:
   http://www.phsanz.com.au/Portals/0/downloads/PHSANZ%202015%20Registry%20report%20Oct%202015%20final.pdf

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.***

   PBAC submissions for older therapies such as bosentan, sildenafil and ambrisentan evaluated change in six minute walk test (6MWT) as the primary efficacy outcome, with secondary outcomes comprising change in WHO functional class (FC), time to clinical worsening and Borg dyspnoea index. More recent submissions however have included composite morbidity/mortality endpoints which the PBAC have considered as more patient relevant. In its review of macitentan, 'The PBAC considered the time to first mortality/morbidity event a more patient relevant outcome than the 6MWD' (Opsumit® (macitentan), PSD March 2014).

   The clinical relevance of the outcomes previously assessed is justified given the evidence was deemed appropriate and acceptable to support inclusion of these treatments on the PBS.

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.***

   Advances in PAH treatments over the last decade have led to the evolution of the treatment algorithm and the advent of combination therapy applied both initially (upfront) or sequentially.

   A recent multicenter, multinational, blinded, placebo-controlled trial titled AMBITION (NEJM, 2015) compared first-line monotherapy with Volibris® (ambrisentan) or monotherapy with Adcirca® (tadalafil) with upfront combination therapy with tadalafil and ambrisentan in de novo WHO functional class II and III PAH patients. The primary endpoint was a composite of clinical failure events (including death, hospitalisation, PAH progression and unsatisfactory clinical status). The study was positive, with a 50% reduction in events in the combination group. In addition, improvements were observed in exercise capacity, rate of satisfactory clinical response and NT-proBNP plasma levels (Galie, NEJM 2015).

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.***

   At its November 2013 meeting, the PBAC noted correspondence from the PHSANZ recommending changes to the then current PBS restrictions for PAH agents. At the time the PBAC noted that 'requests to make PAH agents available for patients with functional class II disease or for use as part of combination therapy would require a submission to be made to the PBAC with evidence demonstrating the comparative clinical effectiveness and safety and cost-effectiveness of therapy in such circumstances'.

   GSK believe the PMR would be better informed if background information or evidence was made available to stakeholders illustrating the QUM issues.

   Whilst the cost-effectiveness of PAH medicines to treat WHO functional class II disease has not been evaluated by the PBAC, there are treatments such as ambrisentan TGA indicated for this clinical severity of PAH.

   As indicated in the response to ToR-4, the AMBITION study addresses a pivotal clinical question regarding the use of upfront combination therapy in PAH (with the specific combination of ambrisentan with tadalafil), however the cost-effectiveness of this treatment approach has not yet been considered by the PBAC.

Conclusion

In consideration that PAH is a highly complex and specialised disease with medicines administered under Section 100 of the *National Health Act* (Highly Specialised Drugs Program) and access restricted to Medicare approved designated centres, GSK recommends a stakeholder forum be held in due course in line with the framework provision of 'significant public interest, complex reviews, or large scale reviews'.

Thank you for your consideration of this input.

References:

Galie N et al. 'Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension'. NEJM 2015; 373: 834-44.

Galie N et al. '2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension'. European Heart Journal 2015; doi:10.1093/eurheartj/ehv317.

Galie N et al. 'Updated treatment algorithm of pulmonary arterial hypertension'. Journal of the American College of Cardiology 2013; 62:D60-72.