September 11 2015

PBS Post Market Review Team
Department of Health
GPO Box 9848
Canberra ACT 2601

Re: *'Review of the Guidelines for the Pharmaceutical Industry on Preparation of Submissions to the Pharmaceutical Benefits Advisory Committee'*.

Dear Sir/Madam

Alexion Pharmaceuticals Australia appreciates the opportunity to submit the following response to the Review of the PBAC Guidelines. Alexion is focused solely on the development of breakthrough lifesaving and transformative therapies for patients suffering from "ultra" rare disease. Therefore, our feedback is directed at highlighting where the current guidelines should be amended to improve the fair assessment of such therapies.

Ultra rare diseases provide a far more challenging area of policy than more common conditions and, traditional Health Technology Assessment models, like those applied by the Pharmaceutical Benefits Advisory Committee are not appropriate for assessing therapies for rare disease. They require a different model to adequately assess their value given the rarity of the condition they treat, the ability to generate data through standard controlled clinical trial approaches and the limited patient population being sought.

Alexion and the rare disease community are awaiting the outcomes of the Review of the Life-Saving Drugs Program (LSDP). Along with other stakeholders, we have advocated for changes to the timely evaluation of medicines to treat ultra-rare diseases and the inclusion of 'fit-for-purpose' guidelines and criteria for the fair assessment of therapies for ultra-rare disease.

We highlight below some of the considerations that should be given to improving evaluation of ultra-rare disease therapies within the PBAC guidelines;

1. **New guidelines should provide direction on what decision makers are using to evaluate cost effectiveness and resulting eligibility for any funding program to ensure Australians will have timely access to life-saving treatments for extremely small patient populations globally.**

The PBAC is required by legislation to consider cost effectiveness as part of its decision making process. Although there is no ICER 'threshold' that determines the evaluation of very rare disease therapies, it is an important piece of data required in a submission. In order for sponsors and government to have a fair and rational discussion, all parties need to understand transparently what decision makers are using to evaluate cost effectiveness and eligibility for any proposed program.

This is a critical consideration and is necessary to determine whether a 'fit-for-purpose program under the PBS could be established with viable criteria capable of being met by the rare disease therapies.

2. **New guidelines should recognise the challenges of ultra-rare disease therapies in meeting the evidence standards of more common conditions.**

Most therapies developed for ultra-rare diseases will meet a high clinical need for a poorly understood condition with accepted severe morbidity and mortality. However, the natural history of these conditions is often heterogeneous and not well understood which creates difficulties in designing appropriate clinical trial programmes which can create delays. There are significant challenges in identifying the appropriate clinically meaningful endpoints and as the clinical trial programme progresses, these can change as disease understanding is improved through study. This has implications for the evaluators and sponsors in agreeing to the most appropriate outcome measures for the evaluation and assessment of clinical effectiveness and cost effectiveness of the ultra-rare disease therapies.

Small patient populations with these conditions globally create considerable logistical challenges in running a clinical trial programme. Recruitment of sufficient numbers of patients to produce the robust evidence required by PBAC to prove a therapies benefit is challenging. A large number of trial sites in multiple countries are required since each may only enrol one or two patients – or none at all.

In addition, clinical evidence demonstrating efficacy and safety of ultra-rare therapies is less likely to be generated using standard randomised controlled trials due to rarity of the disease, the serious morbidity and mortality risk, and the absence of any approved alternative effective treatment.

To address these issues, the updated guidelines must recognize other important sources of evidence (including randomized and non-randomised evidence) and a sponsor's commitment to develop the understanding of the condition as part of the risk-share agreement.

- Registration and reimbursement strategies may need to rely heavily on the initiation of Disease/Patient Registries. These registries have been widely accepted by all stakeholders as important however – have been poorly utilized previously.
- Early access programmes implemented by the sponsors are poorly received by PBAC and stakeholders alike and are perceived to create delays in obtaining a listing. However these

provide urgent access to often desperate patients, generate important local data and provide Australian physicians with experience enough to support the development of local funding guidelines.

Further, there could be explicit and pre-agreed criteria for continued funding of medicines linked to the collection of additional information about the medicine's performance. Alexion supports the progress made in utilisation of Managed Access Programs (MAPs) with an agreed framework contained within the guidelines which provides instruction of appropriate use of this risk-sharing measure.

A fit-for- purpose process should be developed by a multi-stakeholder working group made up of Government, physicians, Industry and Rare Disease Patient Representatives to determine the type of data, timelines, and methodology of data collection, analyses and assessment. MAPs should aim to create earlier provisional access to therapies in an agreement that is fair to all parties whilst addressing uncertainty caused by the data available for an ultra-rare therapy. Alexion also notes that other HTA authorities such as NICE (United Kingdom) sometimes provide interim funding to ensure its citizens are able to access innovative therapies rapidly when extended evaluation is required.

3. New guidelines should incorporate fit-for-purpose criteria for assessment of ultra-rare disease therapies

A modified approach would enable the PBAC to adequately reflect that these medicines serve a limited patient population and therefore come at a high cost, whilst also allowing for these therapies to be funded and managed through an existing structure.

A new dedicated section proposed within the existing PBAC submission structure, would optimally contain the following features:

- Entry for ultra-rare disease medicines, using internationally accepted definitions, for medicines with defined patient populations that offer significant value for patients and the community;
- Appropriate guidance to industry as to the requirements for demonstrating efficacy and justifying price in submissions for a Life Saving Drugs Programme listing;
- A formal pre-submission process to determine whether a medicine is eligible for a LSDP (or alternative dependant on the outcomes of the LSDP Review) funding pathway; and if so, an appropriate user-fee mechanism required for each formal submission in order to offset administrative costs of review;
- Formation of a PBAC subcommittee for rare disease assessments, including physician/s with specific and current expertise in the disease ; and
- Recognition that breakthrough medicines for small patient cohorts will not meet conventional cost effectiveness measures, and that a fit-for-purpose assessment process should be established through a multi-stakeholder working group process.

In closing, therapies designed to treat ultra-rare diseases may not meet cost effectiveness 'thresholds' of PBS and require a different model to adequately evaluate their value due to: 1) the inability to generate data through standard controlled clinical trial approaches; 2) the limited patient population; and 3) the rarity of the conditions. Amendments to the PBAC guidelines to address these unique features will help

to facilitate earlier access to innovative therapies for Australians with high clinical needs, the ultimate goal for all involved.

Alexion appreciates the opportunity to submit feedback on this review and are available to provide further consult if required.

Kind Regards

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