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Dear Sir/Madam,

RE: POST-MARKET REVIEW OF LIFE SAVING DRUGS PROGRAMME

GlaxoSmithKline Australia (GSK) welcomes the timely review of the Life Saving Drugs Programme (LSDP), (herein "the review") and believes that it is necessary to review the access and equity considerations of the programme, and ensure its future sustainability. A comprehensive and robust review informed by public consultation and engagement with appropriate stakeholders is essential to ensure that the LSDP is reformed in such a way that it continues to meet the needs of the community, and will renew stakeholder confidence in the system designed to give access to medicines for patients with rare disease.

GSK has considered the Terms of Reference (ToR) cited on the PBS website and recognises that the review encompasses two primary objectives:

- The application of the LSDP for currently included medicines, and
- The appropriateness of the underlying policy framework and criteria for designating medicines for inclusion within the programme in future.

GSK is broadly supportive of the ToR and has provided comments relating to each individual term below, and would like to highlight the following over-arching points in relation to the review:

- None of the ToR appears to specifically include consideration of the criteria and conditions for funding of the current LSDP. GSK considers that this is a crucial aspect of the evaluation of the ongoing viability of the programme, and trusts that this will be addressed in the review under terms 4 and 6.
- The review should include identification of mechanisms for systematic patient and consumer engagement as stakeholders in the process.
- The review should align closely with Governmental policies regarding rare disease diagnosis, treatment and research.

<u>Specific comments on the Terms of Reference</u>

1. *Review the clinical effectiveness and safety of medicines currently subsidised through the LSDP.*

No comment.

2. *Review emerging clinical treatments and diseases, including those that identify sub-groups by molecular target, which could potentially seek subsidisation through the LSDP in the future.*

GSK believes that horizon scanning of emerging clinical treatments and diseases is a useful exercise, and many sponsors will welcome information regarding the potential eligibility of medicines for future subsidisation through the LSDP. However, greater clarity on the scope and objective of this exercise is required to ensure that stakeholders are able to provide meaningful submissions.

Further, if a formal horizon scanning process is implemented as one of the reforms arising from this review (whereby emerging clinical treatments and diseases potentially eligible for subsidisation through the LSDP are regularly reviewed); consideration should be given to how this process may be managed on an ongoing basis. For example, would Sponsors be routinely approached for input regarding medicines in early development, and within what timeframe (i.e. how far in advance of a potential submission)? The information gained via a regular review may be useful in assessing the capacity of the

programme to respond to new and emerging diseases and treatments, and would also allow Sponsor companies to engage more effectively with the programme and appropriately plan for submissions.

3. *Conduct an international comparison of subsidisation of drugs for rare diseases and the definitions for a rare/ultra-rare disease.*

The challenges of providing access to treatment for rare conditions have been an important area of focus for policy makers in many jurisdictions in recent years. Many HTA agencies, acknowledging these distinct challenges, have adapted their processes or applied unique decision criteria to their standard P&R processes for the assessment of treatments for rare diseases (e.g. Germany, Sweden, The Netherlands). In other countries, treatments for rare diseases are not assessed differently to medicines for more prevalent diseases, but the standard assessment criteria are sufficiently flexible to result in their approval (e.g. France, Italy, Spain).

A report from the Office of Health Economics (OHE) in the United Kingdom reported that by 2009, five European countries had developed national plans on rare diseases, and found that the majority of EMEA-designated orphan medicinal products (OMPs) were available through public health systems in England, Wales, France, Germany, Italy, Spain and the Netherlands (Garau, 2009). The report estimated that of a total of 43 products that had been granted EU Orphan designation at the time, between 70% and 93% had been launched and between 56% and 91% were reimbursed in the 8 countries included in the report. In France, Germany and Spain, 100% of the OMPs that had been launched (38, 35 and 30 products respectively) were reimbursed.

It is important to ensure that Australia is aligned with other developed nations in this key area of health policy; GSK is therefore fully supportive of the inclusion of this ToR in the review. Examples of innovations that have been implemented by other countries and which may be considered when reforming the Australian LSDP include:

- Introduction of a national plan for rare diseases to address issues specific to the management of rare diseases in the national health care system (France, Spain).
- Acceptance of Phase II data to demonstrate clinical effectiveness, in the absence of any Phase III trials (France, Italy).
- Explicit consideration of overall budget impact in the reimbursement of treatments for rare diseases, where the target population is small (Germany, Sweden). In this context, a more uncertain evidence base should be accepted, as the cost of reimbursing a treatment which is not cost-effective is small.
- Application of different cost-effectiveness thresholds for different treatments according to the severity of the target condition, such that treatments for rare diseases may be subject to a higher than normal ICER (England, Sweden).
- Inclusion of criteria beyond cost-effectiveness (e.g. impact on carers and society, consideration of non-health benefits, recognition of the benefit to NHS of research and innovation) in the decision making process, and weighted consideration of different criteria such that not all must be met (England, Scotland, South Korea)
- Implementation of fast-track procedures to facilitate timely access to new treatments, whether OMP or not (France, Italy).
- Control of prescribing to hospitals or specialist centres to facilitate the collection of additional clinical data, which may then be used to re-evaluate the clinical and cost-effectiveness of the treatment (The Netherlands, Italy)

In considering the definitions of rare and ultra-rare diseases, the review should also take into account recent advances in disease-related genomics which enable identification of populations of patients with specific genetic mutations that may be responsive to treatment with particular medicines. These identifiable treatment populations may be small enough to be considered “rare” or “orphan” even when the overall disease is not, and the review should therefore address their inclusion within the programme.

4. *Compare the subsidisation and equity principles of the Pharmaceutical Benefits Scheme and the LSDP.*

GSK considers that the review should acknowledge that standard Health Technology Assessment (HTA) methods (such as those employed by the PBAC) are not appropriate for the assessment of medicines for the treatment of rare diseases. Life-saving drugs should still be subject to formal evaluation, but the assessment process must reflect the difficulty associated with evidence generation in small populations, and the great uncertainty inherent in the results of economic models based on such evidence. Garau (2009) argues that in principle, a higher level of uncertainty should be accepted for Orphan Drugs, *“as the cost of ... endorsing a cost-ineffective medicine is also smaller given the size of the patient*

population." The review should therefore undertake to recommend specific considerations for the HTA of drugs under the LSDP. Particular principles that could be potentially considered by the review for inclusion in the requirements relating to the economic analysis of medicines in the LSDP are outlined below:

- Traditional phase III clinical trials are not feasible for treatments for rare diseases.
- Supporting information regarding the disease such as natural history, epidemiology and standard of care may not be available.
- By definition in the LSDP (criterion 6), no active comparator is available, i.e.: There is *"No alternative drug listed on the PBS or available for public hospital in-patients, which can be used as life-saving treatment for the disease"*. This is echoed in the "rule of rescue" criteria in the PBAC guidelines, the first of which states that *"No alternative exists in Australia to treat patients with the specific circumstances of the medical condition ..."*.Therefore, the only practical analysis for these medicines may be vs. best supportive care (BSC) or placebo.
- Consideration should be given to cost-offsets that may be incurred by management of patients in publicly funded hospitals, in addition to other benefits such as overall impact on patients' Quality of Life (QoL), benefits to carers and the overall societal benefit.
- The threshold ICER should not be considered in isolation, but also in the context of the overall budget impact which, as discussed previously, may be small due to the size of the eligible patient population.

As stated above, GSK considers that this ToR should include a review of the current Criteria and Conditions for Funding of the programme (last updated in 2010). Specific consideration should be given to the appropriateness of criterion 4: *"There is evidence acceptable to the PBAC to predict that a patient's lifespan will be substantially extended as a direct consequence of the use of the drug",* which has been a common reason for rejection of applications made within the programme. Collection of data on overall survival may be impractical for many of the medicines considered under the programme due to the length of time required to observe any incremental benefit for this outcome measure, and the very small patient numbers associated with rare conditions (which make any requirement to demonstrate statistical significance of improved survival unreasonable). Alternative approaches to modelling the estimated benefit of treatment should be accepted in this context, with verification of modelled outcomes via collection of registry data, possibly with the co-operation of multiple countries (as suggested in ToR 7 below).

The review should also give consideration to the apparent inconsistency between the above criterion (number 4) in the LSDP and the fourth criterion in the "rule of rescue" (Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee, v4.4, PBAC, June 2013), which states that the medicines should provide *"a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition"*. The latter would appear to be less problematic to demonstrate than an extension of life, and GSK believes that this requirement should replace the current criterion 4 in the LSDP.

Finally, it is widely acknowledged that funding decisions for treatments for rare diseases should take into consideration equity as well as efficiency. The OHE report (Garau, 2009) highlights that *"From an equity perspective, there are concerns related to how these health benefits are distributed and the extent to which particular disease areas deserve special considerations because of their characteristics, such as seriousness and lack of effective treatment (it may be argued that it is unfair to deny access to new treatments to patients affected with rare diseases with no alternative therapy)."* Any LSDP criteria should also be consistent with the broader policy intent for rare diseases, and consumer perspectives and societal preferences for the equitable prioritisation of health spending should also be taken into account.

5. *Assess the value for money of the medicines subsidised on the LSDP by evaluating the benefit of each drug's treatment outcomes, including in terms of quality of life achieved through the programme, and their cost.*

The objective of including this ToR (which essentially seeks to re-calculate the incremental cost-effectiveness of medicines included within the LSDP) within the review must be clarified. Given that the ICERs have already been determined and deemed to be not cost-effective by the PBAC, re-evaluating them as part of the review is of questionable value. It is likely that the medicines will still be determined to be not cost-effective and therefore ineligible for inclusion on the PBS.

If the intention is that this assessment will inform removal of items from the LSDP, then this should be explicitly stated, together with the justification for doing so. Given the potential inequity and other ethical

concerns which could result from such an approach, an opportunity for Sponsors and consumer groups to engage in discussion with the DoH specifically regarding any affected medicines must be offered.

6. *Review the administration of the LSDP, including the Guidelines with which the programme is administered for each condition, and assess alternative administration systems.*

Review of the administration of the LSDP under this ToR should include examination of the time to listing (as multiple major submissions have often been required, significantly delaying patients' access). The current process of rejection by PBAC prior to consideration under the LSDP is not optimal. Even if sponsors anticipate a rejection by PBAC and seek consideration for LSDP listing in the same submission, positive recommendations from the PBAC for funding under the LSDP are considered by the government on a case-by-case basis, which is time consuming.

7. *Establish a framework for data collection on rare diseases in Australia and assess how this could function internationally.*

Given the rarity of the diseases (i.e. small patient populations) and consequent difficulty in conducting research to satisfy conventional HTA evidence requirements, this would be a worthwhile development, particularly if international cooperation in disease registries for outcome measurement could be achieved. The OHE report acknowledges: *"Given the low and patchy distribution of rare diseases across regions/countries, more cooperation at the European and international level is required to develop robust evidence."* It is important that the Australian healthcare system engages in such initiatives wherever possible.

Conclusion

GSK acknowledges and welcomes ongoing improvements to the Post-Market Review (PMR) programme processes, including those administered to date through the LSDP Review. Transparent, predictable and robust processes are critical to ensuring the PMR programme draws on the expertise of a full range of stakeholders to deliver on stated objectives including improved patient safety and more appropriately targeted medicines. In the context of the LSDP Review, GSK acknowledges:

- the opportunity for stakeholders to comment on draft ToRs;
- the transparency of published information including the role and membership of the reference group;
- an appropriate timeframe for public submissions to be lodged; and
- clarity of next steps and future opportunities to engage in the review (e.g. stakeholder forum and draft report).

GSK strongly recommends the Department continue to work with stakeholders including the pharmaceutical industry to improve PMR programme processes. Further, GSK recommends the Department work with stakeholders to ensure PMR outcomes are considered and interpreted appropriately in line with PBS and access to medicines policy settings, such as the separation of F1 and F2 and the available policy levers to drive the Quality Use of Medicines.

GSK is committed to ensuring the appropriate use of its medicines and appreciates the opportunity to engage as a stakeholder in this review. We would welcome further opportunities to comment on specific aspects of the review as it progresses.

Reference

Garau M and Mestre-Ferrandiz J. Access Mechanisms for Orphan Drugs: A Comparative Study of Selected European Countries. OHE Briefing No 52, October 2009.