1. AVAILABILITY OF MEDICINES FOR RARE DISEASE – EXISTING MEDICINES

TOR1: Review of clinical effectiveness and safety of medicines currently subsidised on the Life Saving Drugs Programme

TOR5: Assess the value for money of the medicines subsidised on the Life Saving Drugs Programme by evaluating the benefits of each drug's treatment outcomes, including the terms of quality of life achieved through the programme and their cost.

Shire has two enzyme replacement therapies (ERTs) listed on the LSDP; REPLAGAL® (agalsidase alfa ghu) for Fabry Disease and VPRIV® (velaglucerase alfa ghu) for Type 1 Gaucher Disease. A separate submission for each product is provided to the post market review with updates of the clinical body of evidence. In summary, longer term evidence for each product continues to show maintenance of clinically relevant outcomes with no new safety risks, in line with the goals of therapy therein demonstrating their continued value and benefits to patients.

Shire requests that patients currently accessing treatment through the LSDP are not disadvantaged as a consequence of the review and continue to have, at a minimum, the current level of access to REPLAGAL and VPRIV.

2. AVAILABILITY OF MEDICINES FOR RARE DISEASE – NEW MEDICINES

TOR 2: Review emerging clinical treatments and diseases, including those that identify subgroups by molecular target, which could potentially seek subsidisation through the Life Saving Drugs Programme in the future

Shire is committed to identifying and developing therapies that meet significant unmet clinical need, including for rare and very rare diseases for which there are no effective treatments. Furthermore, Shire is committed to bringing clinical trials into Australia to enable translation of knowledge into policy and clinical practice.

Currently all pipeline products for rare and very rare diseases are in Phase I or II development programmes. There is no certainty that these medicines will become available in Australia until the clinical trials are complete and have been assessed and granted approval by regulatory and funding agencies.

In January 2014, Shire launched www.shiretrials.com, a dedicated public clinical trials website. Upholding our commitment to the responsible sharing of clinical trials data, Shire Trials lists our current clinical studies, as well as trial results. The site is linked to official websites such as www.clinicaltrials.gov.

3. AFFORDABILITY OF MEDICINES FOR RARE DISEASE

TOR 4: Compare the subsidisation and equity principles of the Pharmaceutical Benefits Scheme and the Life Saving Drugs Programme

Shire supports Rare Voices Australia's request for a National Plan for Rare Disease for Australia.

Orphan drug regulation and reimbursement in Australia has provided incentives for the development and availability of medicines to diagnose, prevent or treat rare and very rare disease. Orphan drug development is a key focus of Shire and the company is the sponsor for five orphan drugs in Australia.

In order to adequately address the needs of the all members of the rare disease community, patients and their families, clinicians, industry and the Government, Shire believes that Australia would benefit from a holistic National Plan for Rare Disease covering policy to support research and development, regulation, diagnosis, treatment and the funding of new therapies. More could be done to integrate the ongoing care needs of patients living with a rare disease.

Improving patient access to medicines for rare diseases

Whilst definitions of rare and very rare disease vary across countries and jurisdictions, with a number using a set disease prevalence to determine rarity, it is commonly agreed that a rare disease is a life-threatening or chronically debilitating disease that only affects a small number of people in the population[i].

Because of the rarity of the conditions, rare and very rare diseases generally have a limited amount of prior information or understanding about the disease before research designed to develop a treatment for the condition is initiated. Often the natural history is not well understood creating difficulties in designing appropriate clinical trial programmes and this can result in delays and added expense throughout the course of therapy development.

Flowing on from these issues is the difficulty in defining clinically relevant endpoints. Using Fabry disease as an example, there have been over 400 different mutations observed in the gene causing Fabry disease[ii]. The correlation of genotype with disease manifestation and progression is still not well understood and this has remained a subject of intense ongoing research. This has implications for study design in terms defining patient's inclusion criteria and biomarkers as clinical endpoints. The uncertainty associated with the use of biomarkers to predict clinical outcome presents difficulties for industry, regulatory and funding agencies alike.

Furthermore, there are considerable logistical challenges associated with conducting global trials in small patient populations. Sponsors often struggle to recruit sufficient numbers of patients to participate and, because of the rare and catastrophic nature of the conditions, it is often not possible to obtain ethics approval to conduct a trial involving a non-active comparator arm. Issues relating to clinical trials mean that for products targeting rare and very rare disease, it is often not possible to show the level of evidence to support the clinical outcomes that are available in more common conditions.

Finally it must be acknowledged that while these therapies may be required to treat small patient populations, the development cost remains comparable to other therapy development programmes. This means that the unit cost of these therapies is often considered high as companies are required to re-coup these costs from a much smaller patient base. Given these specific issues, fit for purpose assessment processes must be put in place to adequately assess the value and nature of evidence that is feasibly generated for rare and very rare disease therapies.

<u>Delays in funded access may impact patient outcome</u>

For those therapies that have successfully negotiated Australia's funding system, the McKell Institute reports that Australians are waiting 2-4 years longer than comparable countries for access to these therapies for rare diseases. Emerging long-term data for currently reimbursed therapies via the LSDP suggests that early intervention is helpful in reducing morbidity and mortality.

<u>Shire recommends a transparent Multi Criteria Decision Analysis (MCDA) process</u>

There has been significant discussion in the literature about the problems of HTA alone for rare and very rare disease therapies. MCDA includes a broad set of

approaches and methods to guide decision making while accounting for the trade-off between multiple criteria. MCDA involves the systematic definition of criteria relevant to a decision, the performance of options against these criteria, and in some instances the weighting of criteria to produce an overall value metric.

MCDA has a number of advantages that would be valuable to the assessment of therapies for rare and very rare disease by enabling:

- The transparent and systematic consideration of multiple criteria, facilitating HTA to go beyond cost-effectiveness and to capture factors such as equity of access, disease rarity and severity, benefits to caregivers etc;
- The reflection of stakeholder preferences through, for example, the elicitation of public or patient preferences to inform criteria weights.

Such an approach is increasingly being adopted around the world with interest in its application being shown by the European Medicines Agency, the Institute for Quality and Efficiency in Health Care (IQWiG) in Germany, the Canadian Agency for Drugs and Technologies in Health (CADTH) and the Department of Health in the United Kingdom.

Work should be undertaken to further incorporate MCDA into the assessment and reimbursement decisions for therapies for rare and very rare diseases. This work should address two key questions. First, which criteria should be included in the MCDA? It is important the answer to this question considers MCDA requirements, such as avoiding double counting, the nature of therapies for rare and very rare disease, such as evidence limitations, and how to include those factors considered by conventional HTA, such as cost or cost-effectiveness. Second, how should this evidence inform decision-making? For instance, how should the relevant criteria be weighted and by whom? How should the opportunity-cost of investing in new technologies be taken into account?

4. ACCESSIBILITY OF MEDICINES FOR RARE DISEASE

TOR 6: Review the administration of the Life Saving Drugs Programme, including the Guidelines with which the program is administered for each condition, and assess alternatives

A proposed administration structure is provided in Attachment 1. A key tenant of this proposal is that under Australia's universal healthcare system, patients with rare

diseases are entitled to the same quality of treatment, if such treatment exists, and that systems for management and reimbursement of these treatments should reflect the unique nature of rare and very rare disease.

It should be noted that this structure will meet the requirements under Australia's universal healthcare system in providing access to therapies for patients with rare and very rare conditions if it includes the following elements:

1. Ethical component: The creation of a specific allocation of PBS expenditure that provides funding for these conditions. Due to the rarity of disease, the overall budget impact will remain low;
2. Value component: A well-defined assessment process to determine:
    a. What therapy areas constitute very rare disease;
    b. Specific understanding of how these products should be assessed and the creation, following consultation with stakeholders, of defined criteria for assessment;
3. Societal component: Establishment of a committee of clinical experts in rare disease. This committee should also include representatives of the rare disease patient community.

5. MONITORING OF MEDICINES FOR RARE DISEASE

TOR7: Establish a framework for data collection on rare diseases in Australia and assess how this could function internationally

Shire supports the need for effective data collection on rare diseases and, in the area of the lysosomal storage disorders, Shire is currently running the Fabry Outcome Survey (FOS) and Gaucher Outcome Survey (GOS) internationally. Shire has dedicated the needed infrastructure to continue to manage and fund FOS and GOS and remain committed to continue to disseminate data from these registries through congress proceedings and other publications.

In view of the fact that there may be other registries in existence or in development, Shire would be open to working with centres of excellence to share its data collection instruments / questionnaires in order for one to be able to pool data parameters common to different registries for reporting or publication purposes and, importantly, to assist in meeting the needs and interests of multiple stakeholders through generating information that provides long-term benefits to patients with rare disease.

ATTACHMENT 1: A PROPOSED STRUCTURE FOR DISCUSSION

Shire acknowledges the administrative burden that the operation of the current Life Saving Drugs Programme (LSDP) places on the Department of Health. It is also acknowledged that arguments can be made both for and against a separate funding system for orphan drugs and rare and very rare diseases.

It is Shire's position that a fit for purpose model, based on the existing Section 100 – Highly Specialised Drugs model, provides a workable format for the reimbursement and management of therapies for rare and very rare disease.

In order to ensure a system that adequately addresses the equity principles outlined above, and to ensure the system both remains workable and enables access to novel therapies for rare and very rare diseases, Shire proposes that a new and separate category be created specifically for the listing of these therapies on the Pharmaceutical Benefits Scheme (PBS). For the purpose of this submission such a category will be referred to as Section 200 – Rare and Very Rare Disease Therapies.

Creating a Section 200 would enable the PBS to adequately reflect that these products serve a very limited patient population and therefore come at a high cost, whilst also allowing for these therapies to be funded and managed through an existing mechanism.

In order to qualify for reimbursement under Section 200, potential therapies would be required to undergo a two stage multi-decision criteria analysis. The first stage would be used to define what constitutes a therapy for use in treating a rare and very rare disease, and may include analysis of the following:

- Rarity - size of patient population;
- Seriousness - type of condition (i.e. chronic, lifelong condition); and
- Medical need – clinically relevant outcomes and potential impact on quality of life.

Other potential criteria to provide certainty around the scheme, including:

- Ability to accurately diagnose the condition;
- Criteria for treatment success;
- Ability to provide on-going monitoring of treatment outcomes.

In order to ensure that this section meets the needs of all stakeholders, it is proposed that the scope of these criteria be developed in consultation with all stakeholders.

Once a proposed therapy has been accepted for evaluation under Section 200, sponsors would prepare a submission using the existing submissions pathway for products seeking reimbursement through the Pharmaceutical Benefits Scheme.

Recognising the fact that therapies to treat rare and very rare diseases require a different model to adequately assess their value given the ability to generate data through standard controlled clinical trial approaches, the limited patient population being sought and the rarity of the condition it is essential that “fit for purpose” guidelines be developed to guide the assessment of these therapies rather than relying on existing PBAC guidelines. Shire strongly argues that these guidelines should adopt a MCDA approach and would form the second stage of such an analysis.

Further, to assist in the often difficult task of assessing these products and in light of the requirement for specific expertise within the disease state, it is proposed that a new subcommittee of the PBAC also be formed with the specific remit of assessing submissions for Section 200 listing:

- This subcommittee, like existing PBAC committees, should provide a report to the PBAC to allow them to make a determination on the subsidisation of products seeking listing under Section 200.
- This subcommittee should include clinical experts with experience in the treatment of very rare disease and should include consumer representation from the rare disease community.

Once a decision has been made to subsidise a therapy under Section 200 and in light of the types of products listed and the costs, specific requirements to ensure quality use of medicine could be include:

- Nominating the speciality required to diagnose and prescribe;
- The requirement for diagnosis and initiation of therapy to be done at a recognised centre of excellence;
- Diagnostic procedures required prior to prescription;
- Post diagnosis and initiation on therapy, the opportunity for partnered care arrangements to be made; and
- Defined continuation criteria to allow ongoing access to therapy.

Once this structure is in place, the existing system for authority to prescribe Section 100 products could be directly adopted and also applied for Section 200 products.

Similarly, the supply of medicines could follow the current system for PBS items. Hospitals or other approved sites could order stock directly from the supplier and be responsible for all aspects of quantity for each patient, storage, payment, stock rotation, damage, temperature excursions.

[i] Rare Voices Australia Factsheet (accessed 31 October 2014) http://rva.blob.core.windows.net/assets/uploads/files/A4_RVA_Fact_Sheet.pdf

[ii] Ki-Yeol Lee et al, "A Case of Fabry's Disease with Congenital Agammaglobulinemia" Jrnl. Korean Med. Sci. vol 26 no. 7 (2011); 966-970