Alexion Pharmaceuticals Australasia

response to

TGA Consultation Paper: Orphan Drug Program; 2015 consultation outcomes and 2016 Orphan Drug program proposal

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Alexion Pharmaceuticals, Inc (Alexion) thanks the Therapeutic Goods Administration (TGA) for the opportunity to submit comments on the TGA Consultation Paper: Orphan Drug Program; 2015 consultation outcomes and 2016 Orphan Drug program proposal. Alexion is a global biopharmaceutical company focused on delivering life-transforming therapies for patients with severe and life-threatening rare diseases with no effective treatment options and as such, has a significant interest in the Orphan Drug Program in Australia.

The Orphan Drug program in Australia has been successful in delivering more effective treatment options for rare diseases and Alexion acknowledges the support of the TGA, the Life Savings Drug Program and the Pharmaceutical Benefits Scheme in ensuring Australians with Paroxysmal Nocturnal Haemoglobinuria (PNH) and atypical Haemolytic Uraemic Syndrome (aHUS) have access to an innovative, life-saving medicine.

Alexion agrees with the proposal to adopt EMA criteria, however, does NOT support the process modifications proposed.

It is stated in the Consultation Paper that the process modifications to the EMA orphan program are required in Australia “due to the differences in the funding models of the two regulators”. The rationale/justification for the modifications in this context is not clear. Whilst the burden on TGA resources and the inefficiencies of the current Orphan Drug Designation (ODD) process are appreciated, Alexion believes further simplification of the procedure, including adoption of overseas designations, could more efficiently reduce the regulatory burden for both the TGA and Sponsors and is aligned with the recommendations from the Medicines and Medical Devices Review (MMDR).

**Increased Regulatory Burden prior to a Registration Application**

Alexion have concerns around the following proposals;

1. Requirement to submit the ODD application within 3-6 months of the registration application,
2. Designation lapsing within 3-6 months if an application is not lodged, and
3. Sponsors additionally have to apply for Priority Review/Provisional Approval 10-12 weeks prior to the registration application to be eligible for an expedited pathway

The pre-submission timeline of 3-6 months for an ODD application is restrictive and inflexible and would cause Australia to move further away from harmonization and alignment with the global regulatory environment. In the US and EU, Orphan Drug Designation is requested early in the drug development program (often before phase I) and this proposal would again place Australian regulations out of step with the countries and R&D bases which dominate drug development in EU and USA. It is unclear why this acknowledgement of a Sponsor’s commitment to develop a drug for an ultra-rare/rare disease is not applicable in Australia.

TGA designation of an Orphan Drug should not be deemed as an ‘administrative’ pre-submission step in a registration application. Designation should be valued by all stakeholders from pre-registration through to reimbursement as an instrument that fosters greater collaboration and consultation with healthcare professionals and other government stakeholders as early as possible in the clinical development program. Ensuring Orphan Designation can be achieved early in the
drug development process, as it is FDA and EMA process, would add much value for all stakeholders in rare disease in Australia. Not least of which, it may be of advantage for the DoH and PBAC in their stated policies of seeking stronger managed entry schemes (MES). Earlier orphan designation linked to earlier discussion in the design of drug development for potential MES strategies for therapies for orphan diseases has much potential merit.

As expressed in the previous Orphan Drug Program Review, Alexion believes the TGA’s Orphan Drugs Policy, along with the recommendations of other Government appointed reviews, such as the Post-Market review of the Life Saving Drugs Program (ongoing), should form the core of an Australian Government Rare Diseases Plan. Ultra-rare/rare diseases share many of the challenges of the “new orphans” or “targeted therapies”, however, these diseases face additional challenges. A relative lack in the understanding of disease pathogenesis and pathophysiology, and scarcity of health care professionals (globally) experienced in their diagnosis and management, contribute to a significant delay in timely and accurate diagnosis and management of the disease (as opposed to targeted treatments easily diagnosed with associated biomarker/diagnostic).

For Sponsors to navigate the complex registration regulations and reimbursement pathways, processes, and policies designed for the more common diseases or highly targeted therapies, will only further delay patient access to innovative and potentially life-saving therapies for ultra-rare/rare diseases. This is especially pertinent in the “ultra-orphan” segment, where diseases have patient populations lower than 1 in 50,000 of population (i.e. 20 patient per million of population). These therapies are often designed to treat populations of > 1 – 10 patient per million of population and hence pivotal registration study programs with long term post market research commitments are essential in the advancement of policies in both the FDA and EMEA.

The complexity and wider considerations required to implement “improved market access incentives” for Orphan Drugs are well understood, and Alexion appreciates the TGA’s commitment to independently update the Orphan Drug program, however, it is essential that the principles of Orphan Drug Designation are preserved, to ensure designation continues to reflect the commitment of a Sponsor, and the government, to invest in Australian patients with ultra-rare/rare diseases, despite the unique challenges these medicines face.

**Impact to Sponsors**

Preparation of a TGA application for Orphan Drug Designation can be resource intensive, particularly for smaller companies. Whilst the information required by the TGA is essentially a duplication of EU (or US) information, the information in the EU/US ODD packages is often not current at the time prior to the Australian registration application (having been filed many years earlier to the EMA and US FDA). The ability to file for ODD at the time of EU/US designation will significantly reduce this burden. Alexion wishes to note that the EMA and US FDA have a common application form for Orphan Drug Designation that could be utilized by the TGA to harmonize the application process for companies.

Contributing to the pre-submission regulatory burden, it was stated in the consultation paper that:

*Lodgment of registration application with orphan status can occur through any of the registration pathways that are either currently available, or the priority or provisional*
Therefore, in addition to submitting the Orphan Drug Application, and if applicable, keeping it valid, in the months prior to a registration application, Sponsors must also submit a formal application to request Priority Review/Provisional Approval.

Alexion represents smaller biotechnology companies, which in fact, make up half of the Sponsors owning ODDs in Australia. Resources (both people and budget) are limited compared to the larger companies, and these additional requirements likely to be required at a time when companies are still working with major Regulators, will place additional pressure on resources. The increased regulatory burden could result in Sponsors in the small biotech sector delaying submissions in Australia and hence could have the unintended consequence of delaying access to globally approved therapies for Australian’s with life threatening rare diseases.

It was not clearly defined whether the “application and evaluation” fee waiver that will be retained for Orphan Drugs, will apply to the Priority Review fee being proposed in the concurrent Consultation Paper “Expedited pathways for prescription medicines”. In light of the lack of other “market access” incentives that overseas regulations offer, such as data exclusivity provisions and tax incentives, Alexion believes TGA designation should automatically qualify the registration application to the expedited pathway to be implemented for Priority Review/Provisional Approval.

In conclusion, Alexion strongly proposes that Sponsors retain the flexibility to file for Orphan Drug Designations (ODD) at any stage during drug development and that TGA ODD automatically qualifies the registration application for expedited review.

Alternative designation proposals

The implications for TGA resources can be appreciated from the Consultation Paper report which states that “34% of Sponsors had not lodged a registration application within a 5-year period (of Orphan Drug designation)”. However, there are alternative options to ensure the TGA are kept informed of Sponsors’ intentions and the ODD status remains valid, that do not set rigid pre-submission criteria and expiry terms to designations:

- The TGA recognize overseas designations from comparable overseas regulators (CORs), such as the EMA and US FDA. A “recognition” process currently exists in Switzerland,
- Sponsors provides annual updates, as per the US (refer to 21 CFR 316.60) and/or
- If, after five years, a Sponsor has not applied for registration, the TGA can withdraw the designation. Five years allows enough time for Australian Sponsors to file the NDA after an EU procedure.

Other comments on proposed criteria/recommendations

Timelines

Whilst the paper proposed defined timelines for Sponsors to apply for Orphan Drug Designation and set periods in which the designation would lapse, the TGA did not clarify the evaluation time for designations. Alexion propose the review period should remain consistent with the current
process, 20 working days. This is aligned with target timeframe proposed in the Consultation Paper "Expedited pathways for prescription medicines" for priority review requests.

**Orphan criterion 2: no existing treatment or significant benefit over existing treatment**

Alexion supports the obligation for Sponsors of Orphan Drugs to demonstrate the drug addresses an unmet clinical need or will provide a significant benefit over existing treatment.

The Consultation Paper stated that almost half of EMA applications (~45% - Morel 2016) did not need to demonstrate significant benefit at the time of ODD application, suggesting almost half of the designations were for novel treatments. Therefore, should the TGA ‘recognize’ overseas designations from comparable overseas regulators (CORs), almost half of the applications could be a simple ‘recognition/adoption” process, with Sponsors only required to demonstrate/justify a similar prevalence would apply in Australia.

The ‘recognition’ of overseas designations from CORs, is applicable also for designations where significant benefit over existing treatments (Australian standard of care) is to be established, as both the EMA and US FDA have similar criteria. The US regulations require Sponsors to demonstrate the “possibility that the drug makes a major contribution to patient care” and in the EU, the EMA’s Committee for Orphan Medicinal Products (COMP) assesses significant benefit at the time of ODD application (early in a medicine’s development) based on assumptions, and again, at the time of marketing authorization.

Alexion can see the benefit of the proposal to allow the TGA’s Principal Medical Adviser to seek external expert advice (including from the Advisory Committee for Medicines) however, this pathway should be reserved for exceptional circumstances only, for example, where an overseas Regulators has NOT designated Orphan Drug Designation, or clinical practice differs from that assessed by the COR. It could be assumed that this was the intent of the recommendation; however, the Consultation Paper did not detail this ‘pathway’, including the impact on evaluation times, especially in light of the tight pre-submission deadline proposed.

Alexion is supportive of this process modification, provided it is not the default pathway for designations seeking to improve treatment outcomes for ultra-rare/rare diseases and not at the detriment of evaluation/approval times.

**Orphan criterion 3: medical plausibility and biomarkers**

Alexion supports retaining the concept of medical plausibility; the process aligns with the EU criteria, where the distinct condition is defined in terms of the specific characteristics, e.g. pathophysiological, histopathological, clinical characteristics.

**Consultation item 4: paediatric populations**

As most rare diseases are diagnosed in childhood and approx. 30% of children with rare diseases will die before the age of 5 years, Alexion, with the TGA, will continue to support access, reduce off-label use and improve data collection in our most vulnerable of the small patient populations.
About Alexion

Alexion is a global biopharmaceutical company focused on developing and delivering life-transforming therapies for patients with devastating and rare disorders. Alexion is the global leader in complement inhibition and has developed and commercializes the first and only approved complement inhibitor to treat patients with paroxysmal nocturnal haemoglobinuria (PNH) and atypical haemolytic uraemic syndrome (aHUS), two life-threatening ultra-rare disorders. In addition, Alexion's metabolic franchise includes two highly innovative enzyme replacement therapies for patients with life-threatening and ultra-rare disorders, hypophosphatasia (HPP) and lysosomal acid lipase deficiency (LAL-D). Alexion is advancing the most robust rare disease pipeline in the biotech industry with highly innovative product candidates in multiple therapeutic areas. Australian PNH patients can access Soliris under the Life Saving Drugs Programme (LSDP) and Australian aHUS patients can access Soliris under Section 100: Highly Specialised Drugs Program of the Pharmaceutical Benefits Scheme (PBS).

Alexion supports advocacy groups and charitable foundations in Australia, including the PNH Support Association of Australia (PNHSAA), aHUS Patient Support Group Australia (aPSGA) and Rare Voices Australia (RVA) as an Industry Roundtable Partner

Alexion’s approach to serving patients is driven by education and a passion for understanding and meeting the unique needs of patients and families suffering with rare diseases. These include disease education programs to raise awareness among physicians, and diagnostic initiatives to reduce the multi-year delays that patients with rare diseases often face, even when a safe and effective therapy is available.

Alexion partner with private healthcare organisations, policymakers and governments around the world so that patients with rare diseases have access to the therapies they need. Our commitment to the lives of patients and families struggling with severe, ultra-rare, and life-threatening diseases is what drives us to work harder.