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Orphan Australia and the Orphan Drug Programme

Submission to the House of Representatives Health and Ageing Inquiry into Health Funding

EXECUTIVE SUMMARY

Orphan Australia commends the Government for changes to the orphan drug programme that have resulted in an increase in orphan drug registrations. However, PBAC evaluation criteria have an unfortunate and unintentional consequence within an otherwise solid pharmaceutical benefits scheme. Selected aspects of PBAC evaluation criteria are to the detriment of Australians with rare and ultra-rare diseases reliant on orphan designated drugs. This corollary runs counter to the good work the Australian Government has done thus far to ensure these patients are not further deprived or disadvantaged.

Due consideration must be given to the mechanisms for funding orphan designated drugs to ensure Australians with rare and ultra-rare diseases are not disadvantaged. Orphan Australia is asking the Inquiry into Health funding to consider alternatives to the funding of orphan designated drug. Such alternatives should not diminish the integrity of the evaluation process and should take fair and reasonable account of the difficulty orphan drug sponsors have in meeting the PBAC cost-effectiveness criteria specifically developed to deal with large patient populations and significant PBS expenditure.

ORPHAN AUSTRALIA

Orphan Australia, founded in 1995 and based in Melbourne, is a small Australian pharmaceutical company committed to searching for and financing niche and orphan pharmaceutical products to treat life threatening and rare diseases where current therapy is unavailable or inadequate.

Orphan drug designation applies to pharmaceutical products used to treat rare and ultra rare diseases affecting fewer than 2,000 individuals at any one time.

According to World Health Organization estimates, approximately 5000 rare diseases affect human beings around the world.

Some diseases affect very few patients, for example Fabry Disease affects 34 to 56 people in Australia annually. Other diseases have larger patient populations in Australia: 260 people are estimated to have primary biliary cirrhosis; 360 to 420 people have thalassaemia major; 510 people have pulmonary arterial hypertension; and 1200 people have essential thrombocythaemia.

The Problem Facing Orphan Drugs

Orphan designated drugs are specifically designed to treat rare disease, such as those mentioned above, and incur similar development costs to most other pharmaceutical products. Accordingly, they attract a disproportionately higher 'cost per patient' compared to conventional pharmaceuticals used to treat more common diseases with much larger patient populations.

Understandably, this can adversely affect the commercial viability of many orphan drugs and has deterred sponsors from registering them with the relevant regulator. In 1998 the Federal Government identified the high costs involved in obtaining TGA marketing approval for such drugs and launched the Federal Government Orphan Drug Programme. This programme has had a positive impact on orphan drug registrations.

The Federal Government Orphan Drug Programme however, did not address the other key problem orphan drugs face – the difficulty in obtaining a PBS listing. Most orphan designated drugs are not

subsidised by the PBS. A considerable number of Australians with rare diseases are consequently denied access to orphan designated drugs, and many are denied access to affordable orphan drugs.

The costs associated with providing patients with orphan drug treatments for life threatening and rare diseases are evident even at the initial stage of TGA registration.

A significant number of orphan designated drugs are not TGA registered because of the prohibitive cost in preparing a registration dossier; the PBS history of orphan designated drugs; and the limited potential commercial return. The cost of preparing a TGA dossier and a PBS submission varies according to the product and prevailing circumstances. It is conservatively estimated that the cost to *Orphan Australia* of preparing the above is between $150,000 and $225,000. This is exclusive of any related TGA or PBAC charges, licensing fees, clinical trial costs and marketing costs.

For example, a clinical trial costs in excess of $500,000. However, due to the relatively small number of patients with rare diseases in Australia, it would be impossible to recruit enough patients to conduct a clinical trial that satisfies PBAC criteria.

Indeed, the Australian Orphan Drug Program (1998) acknowledged that these drugs are usually not commercially viable as the financial return is small compared to the costs involved. Patients with a clinical need for these orphan designated drugs are therefore already significantly disadvantaged.

In some cases *Orphan Australia* makes these products available to small patient numbers in accordance with strict TGA Special Access Scheme (SAS) protocols. Strictures placed on these products restrict any marketing, discussion or promotion whatsoever of the product in Australia and are therefore made available only on direct clinician or hospital request.

The Difficulty in Obtaining a PBS Listing

To register a drug under the Federal Government Orphan Drug Programme, a sponsor must first seek orphan drug designation. Once granted, the sponsor may submit an application for registration.

Orphan designated drugs meet the same stringent standards of clinical efficacy, safety and quality as regular registered products.

Of the 90 pharmaceutical products with designated orphan drug status, 51 are listed on the Australia Register of Therapeutic Goods. Seventeen of these orphan designated drugs are also listed on the Pharmaceutical Benefits Scheme (PBS). Four of the 17 drugs are blood plasma derived products and thus funded through specific and unique funding mechanisms between Government and suppliers.

As a class, orphan drugs have a high failure rate in PBAC applications. In evaluating PBS submissions the PBAC considers: comparative effectiveness; comparative safety; and comparative cost-effectiveness, against agreed comparators to determine 'value for money'. The comparator is, in most instances, another product already listed on the PBS or placebo.

Successful PBS submissions are generally approved on a cost minimization basis – similar costs for similar health outcomes. Orphan designated drugs are, by their very nature, high cost and low volume. The PBAC cost-effectiveness criteria, which were specifically developed to evaluate cost-effectiveness of pharmaceuticals for use in relatively large patient populations, often deem the orphan designated products unsuitable for listing.

Level 1 double blind randomised controlled trials are recognised as gold standard data in PBAC submissions. The PBAC looks more favourably on such evidence. However, by the very nature of orphan designated drugs, the associated studies are less likely to provide the requisite data to clearly demonstrate cost-effectiveness. Inherent features of orphan drug studies are: small patient numbers; non-randomised; non-comparative; use of surrogate markers; and of short duration. Furthermore, such trials may not be of sufficient duration to show a survival benefit.

In addition to the PBS challenges above, the success of a PBS application often depends on whether or not there is a current treatment option. Paradoxically, the likelihood of success is further

diminished if the sponsor is seeking reimbursement for a new product for which there is no alternative treatment. This is exemplified in the PBS history of the following *Orphan Australia* products:

- **Litak** is an *Orphan Australia* pharmaceutical. Litak is indicated for the treatment of *hairy cell leukaemia* and as second-line treatment for *Waldenström's Macroglobulinaemia*. Litak is however only PBS listed for *hairy cell leukaemia*. Litak was the second product listed for this indication and required a 'minor submission' and an agreement by the sponsor to accept a price based on 'cost minimisation'.

  Orphan Australia is not in a position to apply for PBS reimbursement as a treatment for *Waldenström's Macroglobulinaemia* as this would require a 'major submission'. This would include clinical trials specifically to test the cost-effectiveness of Litak against a specific Australian comparator under Australian therapeutic conditions. Notwithstanding the clinical efficacy and patient need for Litak, *Orphan Australia* is not in a position to meet the expense of preparing a PBS submission given the likely risk of failure at PBAC on account of the small patient numbers and relatively small commercial return.

- **Ferriprox** is PBS listed for the treatment of iron overload in children and adults with *thalassaemia major*. The presence of a pre-existing PBS listed treatment enabled *Orphan Australia* to proceed with a PBS submission and agreement to accept a price based on 'cost minimisation'.

- **Agrylin** is used in the treatment of *Essential Thrombocythemia* (ET). *Orphan Australia* has submitted three unsuccessful applications for PBS listing between 2001 and 2003. The PBAC determination of unacceptable cost effectiveness is based on the level of evidence submitted.
  - The clinical trials for the use of Agrylin in ET were designed in conjunction with the US FDA, as part of the Orphan Drug Program in the USA. These were single-arm trials rather than the PBAC's gold standard of randomised controlled trials. Although the data was acceptable for registration purposes in the USA, Europe and Australia it was considered inadequate for PBS listing.
  - The PBAC preferred *Orphan Australia* extend the submission analysis to include data on 'life-years gained' although the PBAC acknowledged that the data to permit this extrapolation were unlikely to be readily available.
  - Despite the clinical evidence suggesting Agrylin adequately reduces the platelet count in the majority of patients, and therefore the associated morbidity, the PBAC was unable to determine the impact on patient-relevant outcomes

- **Ursofalk** is TGA-approved for the treatment of liver diseases such as: *primary biliary cirrhosis; primary sclerosing cholangitis* and *cystic fibrosis-related cholestasis.* Ursofalk is PBS listed for *primary biliary cirrhosis.* There is insufficient data in the form acceptable to the PBB and PBAC to support a PBS application for its use in *primary sclerosing cholangitis.* Notwithstanding the clinical need for Ursofalk, *Orphan Australia* is not in a position to meet the expense of preparing a PBS submission given the likely risk of failure at PBAC on account of the small patient numbers and relatively small commercial return.

What does this mean for patients?

In many cases there is no alternative to an orphan designated drug. Orphan designated drugs provide patients with rare and life threatening diseases an alternative to inadequate treatment options. A number of these drugs provide the only treatment option. For example, **Gliadel** is the only chemotherapy agent indicated for administration directly onto the brain tumour site following its surgical removal.

If patients cannot access these orphan drugs:

- They can die of their disorder or disease. For example, treatments such as **Remodulin** for pulmonary arterial hypertension and **Ferriprox** for thalassaemia major can improve a patient's quality of life and reduce the risk of heart failure.
- They require organ transplant sooner. For example, without **Cystagon** adults and children with nephropathic cystinosis, a rare inherited disorder-affecting adults and children, would progress more rapidly to kidney failure. Access to Cystagon can buy precious time to find a suitable donor, or at best avoid the need for a transplant; **Ursofalk,** used to treat liver diseases can reduce the risk of developing cirrhosis and liver failure, as well as delay time to liver transplantation.
- Doctors prescribe medications 'off label'. For example, hydroxyurea is sometimes prescribed 'off label' for the treatment of essential thrombocythaemia (ET). Hydroxyurea is used as an alternative to the orphan designated drug **Agrylin.** Hydroxyurea is not approved by the TGA for ET. The patient is therefore not being prescribed the best or most effective treatment option for their condition.

It is important to note that *Orphan Australia* brings these niche pharmaceuticals to market based on clinical requests, not to create a market. *Orphan Australia* responds to medical requests rather than driving a market.

The difficulty in providing sufficiently appropriate data to fulfil the PBAC criteria dissuades sponsors such as *Orphan Australia* from responding to medical requests to source and provide orphan designated drugs to treat rare and ultra rare diseases. Consequently, patients with these specific clinical needs with inadequate or no treatment options continue to be disadvantaged.

Conclusion

The total potential cost to the PBS of *Orphan Australia's* orphan designated drugs is less than $10 million annually. This data is based on the assumption that (a) *Orphan Australia's* entire orphan designated drug portfolio obtained a PBS listing and (b) all patients with rare and ultra rare conditions access these orphan drugs in accordance with their respective indications. The data from which this information is drawn is available *commercial-in-confidence* on request.

In the past five years, two reports known to the Federal Government have highlighted the need for greater community access to orphan designated drugs and, in particular the need for further discussions on the PBS process as it applies to orphan designation.

In February 2000, Senator Tambling announced the findings of a review into the Pharmaceutical Benefits Scheme (PBS), which included the following recommendation: *"Further discussions on a mechanism encouraging applications for PBS listing of orphan drugs should occur between the PBAC, the APMA and the Pharmaceutical Benefits Branch"*

In December 2001, consultant Tom Hayes AO completed his report into "The Orphan Drug Programme and Improving Community Access to Effective Drugs for Rare Diseases".

The report acknowledged that certain orphan drugs have been successful in achieving public funding through mechanisms other than PBS listing. The Review noted, *"four products were specialised blood products funded through the special arrangements between the Commonwealth and the States. Another is funded under the life savings drug program through the States. The decision to fund these products has not been made on an assessment of acceptable cost effectiveness according to the guidelines followed by the PBAC."*

Progress has been made, however. Despite these two reports access to a significant number of orphan drugs remains prohibitive for many Australians suffering from rare and life threatening diseases.

Orphan Australia is asking the Inquiry into Health funding to consider the alternatives either within or externally to the PBAC in the funding of orphan designated drugs; such that the integrity of the evaluation process is not diminished and takes fair and reasonable account of the difficulty orphan drug sponsors have in meeting the PBAC cost-effectiveness criteria developed generally to deal with large patient populations and significant PBS expenditure.

APPENDIX I – ORPHAN AUSTRALIA PRODUCT PORTFOLIO

Haemotology and Oncology

- **Agrylin**[1] (anagrelide hydrochloride) is used in the treatment of Essential Thrombocythemia (ET), which is characterised by an overproduction of platelets. Excessive levels of platelets can lead to thickened and slow flowing blood, which has a tendency to cause thrombosis (blood clots). Agrylin prevents overproduction of platelets.
- **Ferriprox**[1] (deferiprone) is PBS listed for the treatment of iron overload in children and adults with thalassaemia major (TM). Those with TM cannot manufacture normal haemoglobin (the oxygen carrying protein in blood). If left untreated children can develop potentially life-threatening heart failure. In the long term it can lead to stunted growth, delayed development, and multi-organ failure. The only cure is a bone marrow transplant.
- **Gliadel**[1] (carmustine) is used to treat newly diagnosed high-grade malignant glioma (brain tumours) following surgery. The wafer strips are applied directly to the tumour site following removal of the tumour, thus ensuring direct delivery of the drug to the target site. Gliadel kills residual cancer cells and /or stops cancer cells growing and multiplying.
- **Litak**[1] (cladribine) is used in the treatment of hairy cell leukaemia and is the only product registered for use as second-line treatment of Waldenström's Macroglobulinaemia (WM), a type of non-Hodgkin's lymphoma. It is PBS listed for hairy cell leukaemia, which is a slow-growing malignant disorder affecting white blood cells. These cells accumulate in bone marrow and spleen preventing the production of normal blood cells. In WM, abnormal lymphocytes in the bone marrow produce an antibody (IgM) that can potentially thicken the blood plasma, causing nosebleeds, dizziness, gum bleeding and blurred vision.
- **Busulfex**[2] (IV busulfan) is indicated for use in combination with other chemotherapeutic agents and/or radiotherapy as a pre-conditioning regimen for haematopoietic progenitor cell transplantation. Haematopoiesis is the process of blood cell production and differentiation. Busulfex is used to restore normal haematopoiesis in patients affected by a number of blood and bone marrow related diseases.

Metabolic Disorders

- **Cystagon**[3] (cysteamine bitartrate) is used in the management of nephropathic cystinosis in children and adults. Nephropathic cystinosis is a rare inherited disorder characterised by the build up of cystine in organs, such as kidneys. This can cause kidney damage and excretion of excess amounts of glucose, proteins and electrolytes, resulting in slow growth, weak bones and progressive kidney failure.
- **Cystadane**[3] (betaine anhydrous powder) is used for the treatment of homocysteine in children and adults. Homocysteine causes cardiovascular thrombosis leading to premature death, osteoporosis, skeletal abnormalities, and optic lens dislocation.

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[1] TGA designated orphan drug.

[2] Product is currently only available under a Special Access Scheme. Orphan designation and registration is pending (PBS application to be considered in due course).

[3] This product meets the TGA criteria for orphan drug designation but was registered prior to the introduction of the relevant legislation and is therefore not included on the TGA's orphan drug list.

- **Adagen**[4] (pegademase bovine injection) is used in the treatment of adenosine deaminase (ADA) deficiency in children and adults with severe combined immunodeficiency disease (SCID). Adagen replenishes ADA, which allows an increase in white blood cells and decreases the risk of infection in conditions such as SCID.
- **Buphenyl**[4] (sodium phenylbutyrate) is used as adjunctive therapy in the chronic management of children and adults with urea cycle disorders (UCD). UCD's cause a build up of waste products, such as nitrogen, which can lead to brain damage and death.
- **Carnitor**[4] (levocarnitine) is used to treat carnitine deficiency in children and adults. A deficiency of carnitine can happen due to long-term haemodialysis and can result in extreme muscle weakness, cardiomyopathy and other related symptoms.
- **Orfadin**[4] (NTBC, nitisinone) is used in the treatment of hereditary tyrosinemia type 1. This condition, usually seen in children, leads to an abnormal accumulation of tyrosine in the liver and can potentially cause severe liver disease and failure to thrive.
- **Sucraid**[4] (sacrosidase) is used to treat genetically determined congenital sucrase-isomaltase deficiency or CSID in children. Children with CSID cannot break down certain sugars and starches. Symptoms include diarrhoea, dehydration, malnutrition and failure to thrive. The condition usually improves with age.

Cardiovascular

- **Remodulin**[1] (treprostinil sodium) is used to treat Pulmonary Arterial Hypertension or PAH (i.e. blood pressure in the lungs is higher than normal). Remodulin widens the blood vessels supplying the lungs and the body and also stops clotting. Increased blood pressure in the lungs places a strain on the heart causing less blood to be pumped into the lungs, resulting in shortness of breath, tiredness and as heart failure develops, swelling in the feet and abdomen.

Gastro Intestinal

- **Ursofalk**[3] (ursodeoxycholic acid) is TGA-approved for the treatment of liver diseases such as primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and cystic fibrosis-related cholestasis. It is PBS listed for PBC. All these conditions impact on flow of bile and bile precursors leading to a build up in the liver causing conditions such as cirrhosis and liver failure.

Central Nervous System (CNS)

- **LAX101**[1] (ethyl eicosapentaenoic acid) is an innovative agent undergoing development for the treatment of Hungtingdon's Disease (HD). HD is a progressive and debilitating neurological condition that gradually renders the patient incapable of normal day-to-day function including employment and self-care. Mean age of onset is about 40 years with a duration of15-20 years.

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[4] Product is only available through a Special Access Scheme. Despite meeting TGA criteria for orphan drug designation there is no incentive to register the product (i.e. very small patient populations and relatively high cost of preparing registration dossier).