Vertex's response to the Public Consultation on the Post-market Review of the Life Saving Drugs Programme

Executive Summary

In this submission, we set out Vertex's response to the Post-Market Review of the Life Saving Drugs Programme (LSDP). LSDP is an important and vital part of the Australian approach to ensuring access to treatments for rare diseases. However, the wider system needs to be tailored to the unique characteristics of medicines for rare diseases to ensure that Australian patients have access to all medicines for rare diseases as originally intended, and to redress the historic lack of treatment options for these diseases. We highlight the following key conclusions:

- LSDP is international best practice, but the system needs to evolve to ensure an appropriate review for all medicines for rare diseases;

- The DOH/PBAC needs to provide clear guidance for Sponsor companies (at pre-submission meetings) regarding the most appropriate scheme and the corresponding process.

- Given the need to have a holistic system that includes coverage of all rare medicines, this could include the LSDP and existing Section 100 but also provide a tailored pathway for products that would otherwise fall in the "missing middle".

- The process should incorporate a fast, flexible HTA review that leads to rapid access to innovative medicines for patients in need (as demonstrated in other countries):
  - Special (PBAC) subcommittees should be created which would include subject matter/therapeutic area experts;
  - The process should not be confined to PBAC's 17 week timetable; e.g. could meet in special session; and
  - The process should be based on Multi-criteria Decision Analysis (MCDA) or have appropriate exemptions.

Vertex is a global biotechnology company that aims to discover, develop and provide to patients innovative medicines so people with serious diseases can lead better lives. In addition to our clinical development programs focused on cystic fibrosis, Vertex has more than a dozen ongoing research programs aimed at other serious and life-threatening diseases.

In Australia, ivacaftor (Kalydeco) is approved for patients 6 years or older who have the G551D or other gating CFTR gene mutation.[i] In addition to Kalydeco, which has been approved for use in 18 other countries[ii], Vertex also has further molecules for cystic fibrosis in the pipeline.

Designing a mechanism that provides patient access, aligns prices to values, and provides sustainable funding for rare medicines is challenging and an area of much debate. Over the last 19 years, the Life Saving Drug Programme (LSDP) has provided vital access to patients suffering from rare diseases[iii] and ensured access to the types of product that are inevitably going to fail to meet conventional cost effectiveness analysis undertaken by PBAC. However, as with any regulation, it is important to assess whether it is working as effectively as it can and meeting all the objectives it was given, that is, to continue to provide "subsidized access to expensive medicines" whilst ensuring an adequate balance between "access equity, and value for money."[iv]

Vertex welcomes the opportunity to contribute to the debate on the Post-market Review of the LSDP. Vertex has only responded to the issues/topics for which it has specific contribution to make to the debate.

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

Before turning to the future, it is useful to review the benefits of the Australian orphan drugs (OD) framework; particularly, the objectives of the orphan drug regulation, but also the consequence this may have for the long term sustainability for funding of ODs.

Objectives and impact of the orphan drugs regulation

In 1998, Australia introduced a special regulatory framework for orphan medicines designed to help manufacturers to overcome the risky nature of drug development associated with small patient populations, specifically a prevalence of 2,000 patients/subjects or less in the Australian population. In addition, the need for funding was recognised, hence the development of the LSDP. This has been successful in encouraging new products and since these incentives were introduced, there has been a significant increase in research and development for medicines for rare diseases. This has not only contributed to impressive progress in treating certain diseases but has also translated into dramatic improvement for patients and their families as well as improving quality of life and survival.[v]

Although the debate is often framed in terms of 'orphan diseases' or 'medicines for rare diseases', it is important to look within these categories at the diversity of the conditions. Looking at emerging products (see annex), we can observe medicines for a variety of diseases such as Haemophilia A, Haemophilia B, or Morphios A syndrome or Multicentric Castleman's disease which have different levels of prevalence and which differ in terms of whether there are reasonable therapeutic alternatives, the types of patient affected and whether they are targeted to particular sub-groups. It is therefore important to recognise that societies' preferences are multi-dimensional reflecting the number of patients affected by the disease but also severity, availability of existing treatments and whether it affects particular groups.

The implication of this is that the criteria for inclusion should allow a trade-off across these preferences. This should ideally be aligned with other systems internationally (allowing consistent incentives) and consistency over time (given the length of time to develop a medicine for a rare disease is similar to other products). For example, there is no single definition for rare diseases that is accepted worldwide.[vi] As illustrated in Table 1 in the annex, these definitions typically include a criterion of disease incidence or prevalence. In Australia, a condition is considered rare if it affects 2,000 individuals in the entire population (approximately 1 in 10,000). This is already narrow by international standards, with the EU a condition defining a 'rare' condition if its frequency is 1 in 2,000 and only ~1 per 1,500 in the United States. Although, the term ultra-rare was developed by NICE in the England in practice no other countries have adopted an ultra-orphan category and even England has chosen to adopt a flexible approach.[vii] What this shows is that there needs to be a spectrum of incentives rather than a binary system. Rather than having a rare and ultra-rare designation, pricing and reimbursement agencies should consider how rewards should be tailored based on societal preference for treating rare diseases.

Sustainability of funding

Vertex also recognises that the increasing number of medicines for rare diseases brings concerns about the sustainability of funding.[viii] Given the incentives were only introduced in the last twenty years; an increase in the number of medicines is the inevitable consequence of the success of the rare diseases framework. Indeed, this has been predicted for some time with forecasts from five years ago suggesting there will be approximately 100 new ODs between 2009 and 2019, equating to about ten new OD per year (the same as the last five years).[ix] In reality, given the significant risk (similar to those of product for large patient populations) in researching and developing medicines for rare diseases, the number of new medicines will vary from year to year and it is impossible to predict spending with any certainty. This means spending on rare disorders will need to increase over the next few years and have a degree of flexibility. However, it is vitally important that resources are allocated to medicines for rare diseases consistent with society's preference for providing the most vulnerable patients access to treatments and recognising that despite the progress that has been made, there is wide agreement that there is still significant unmet need with over 6,000 rare diseases that do not have a single approved treatment.[x]

Conduct an international comparison of subsidisation of drugs for rare diseases

Although Vertex appreciates that governments are often faced with stretched healthcare budgets, it also believes that there is a danger that the unique characteristics of orphan medicines that justify a distinct regulatory pathway are forgotten when the product is applying for reimbursement.

A joined up system is needed that recognises these unique characteristics across both the regulatory regime as well the reimbursement regime. In fact, through the creation of the LSDP, Australia has recognised that there is a need for a system of pricing and reimbursement that allows new orphan medicines to reach the patients. As in Australia, some other countries have also developed similar types of hypothecated fund to ensure coverage of medicines for rare diseases:

- Scotland – the Rare Conditions Medicines Fund established in January 2013 to cover orphan drugs (medicines for illnesses which affect fewer than 1 in 2,000 people). Applications for products "not recommended" by the SMC would need to demonstrate failure to respond to current treatment, or no other alternative.[xi] It has recently been announced that this will be replaced by the New Medicines Fund with expanded funding.
- New Zealand - PHARMAC is proposing a Contestable fund for medicines for rare disorders and there is an ongoing consultation.

However, it is important to note that even where these are targeted on smaller patient populations, such as Scotland's New Medicines Fund, they are not limited by prevalence and for products not eligible for the fund, a tailored process is applied.[xii]

Whilst it is clear that the establishment of a separate process for orphan drug reimbursement with a ring-fenced budget can make sense for some types of orphan medicine (and will typically focus on less prevalent diseases), it should also be recognised that this is not the only system. In fact, over the last twenty years, different countries have developed a variety of orphan medicine frameworks to provide access to patients with rare diseases. Across these international markets, we think there are two other important approaches that merit consideration:

1. Recognising the special characteristics of medicines for rare diseases, some countries such Germany have exempted these products from undergoing parts of the HTA process. There is a recognition that HTA cannot be applied in the same way as other products which justifies an exemption from parts of HTA process. For example, Germany has an annual revenue threshold of €50 million, below which medicines undergo an abbreviated rather than full AMNOG assessment process, avoiding the requirement for comparator benefit assessment. This simplifies the process and ensures rapid patient access but also avoids duplication of effort. As a result, Germany is classified as having "high" level of access to ODs (more than 54 ODs out of 72 given marketing authorisation in the EU were reimbursed as of 2014). [xiii]
2. Other countries such as England[xiv] have chosen to maintain value assessment requirements for ODs for the purposes of recommending reimbursement; however, this is tailored to the unique characteristics of ODs using multi-criteria decision analysis (MCDA). This enables decision-makers to explicitly trade-off various factors against each other, such as the seriousness of the condition and the lack of suitable treatment alternatives, alongside cost-effectiveness.

Common to all of these systems is a recognition that applying the same approach of cost effectiveness to medicine for rare diseases as other types of medicine will deny patient access and reduce any incentive to bring these medicines to market. Indeed, unless a wider assessment of value is taken into account, perverse situations can occur where products demonstrating significant clinical benefits, improving the survival of patients, are more likely to be rejected because increased survival increases on-going healthcare costs.

Compare the subsidisation and equity principles of the Pharmaceutical Benefits Scheme and the LSDP

Subsidised access to orphan drugs in Australia has taken place through two main programs:

- The LSDP, aimed at rare medicines that are not cost effective, however, in practice there is some confusion as to whether the LSDP is intended for rare or very rare diseases. Since the LSDP was created, only 12 products have sought LSDP funding, 10 are currently reimbursed covering 7 disease areas. According to some authors, the LSDP has essentially narrowed its access to funding down to only very rare diseases.[xv]

- Section 100 of the PBS i.e. the Highly Specialised Drugs Program[xvi]. However, to be considered by the PBAC for inclusion in the programs, the treatment must demonstrate clinical advantages over existing treatments as well as cost effectiveness in comparison to these treatments.

However, it should not be a surprise that many products which carry an orphan drug designation by TGA are not cost effective if traditional rules of cost effectiveness are applied. In fact, the orphan drug category was created by the TGA in order to recognise the cost and risk involved in the development of these medicines is high and given the patient population these product would not otherwise be developed. This may be most extreme for medicines that could be categorised as "very rare" but nevertheless applies to all medicines for rare diseases.

This serves to highlight that there is a danger of a "missing middle" in the way medicines for rare diseases are subsidised in Australia. LSDP appears to only cover medicines for very rare diseases, but there is no approach for medicines with a larger patient population that are also inevitably going to be above standard cost effectiveness thresholds for medicines treating more common diseases. There are many medicines for rare diseases that are inevitably not cost effective by standard techniques given they serve relatively small patient population, and yet these are not eligible for a separate evaluation framework or subsidisation through a hypothecated fund such as LSDP. There is therefore a need for a third way – a tailored approach similar to Section 100 that allows for the unique characteristics of these medicines.

The DOH should consider introducing a new reimbursement pathway with a faster, more flexible HTA review, which would lead to rapid access to innovative medicines for patients in need. This could work by creating a new pathway for medicines for rare diseases that neither meet the requirement for LSDP nor meet the requirement for cost effectiveness set by section 100. Products in this channel could be exempted from parts of the HTA process such as in Germany (i.e. no comparator benefit assessment) or could still have a form of HTA but one based on MCDA as discussed above which would take into account the societal preference for access to different types of medicine for rare diseases. This new form of HTA could be led by special (PBAC) subcommittees which would include subject matter experts in specific therapeutic areas as well as patient representatives, called in for special sessions and therefore would not confined to PBAC's 17 week timetable. One example of this can be found in Scotland, where the Scottish Medicines Consortium convenes a Patient and Clinician Engagement (PACE) group which was introduced in May 2014 as a way for patients and clinicians to have a stronger voice in orphan (5 in 10,000) and ultra-orphan (1 in 50,000) medicine assessments. SMC considers "modifiers" in the HTA process that allows for higher uncertainty and cost per QALY.[xvii]

Review the administration of the LSDP

One of the main challenges associated with the administration of the LSDP is both the lack of clear and adequate guidance for sponsor companies regarding the reimbursement process, and as a result, the delay in access caused by complex and lengthy negotiation (often linked to lack of clarity/expectation setting over the process). Looking at the 10 products currently listed on the LSDP, the average time from the first PBAC decision of a product until LSDP funding was 19.7 months and 15.2 months from positive LSDP recommendation to funding initiation.

Of particular concern is the process for determining coverage under the PBS or under the LSDP. Formally, the coverage decision is straightforward "The drug must be accepted as clinically effective, but rejected for PBS listing because it fails to meet the required cost effectiveness criteria." However, in practice there are a variety of different approaches used to achieve cost-effectiveness of the medicine for non-orphan medicines and when applied to orphan, this introduces some ambiguity into whether a product has failed the cost effectiveness criteria or not.

As a result, the DOH/PBAC should provide sponsor companies with clear guidance (at pre-submission meetings) regarding:

- The type of scheme the product is being expected to be listed in (e.g. LSDP, Section 100, normal PBS or a new rare disease pathway). This clearly requires greater clarity from PBAC on:
    - the definition of "failing to meet the required cost effectiveness criteria";

- the timeline which determines the interaction between PBAC and LSDP;[xviii]
- the transparency of the approval process.[xix]

- The process and conditions by which the product is expected to be funded. For example through a risk-sharing agreements (e.g. pay for performance).

Vertex understands that budget concerns lead to challenging pricing and reimbursement negotiations. This can lead to the exploration of alternative options, however, an ambiguous process that results in unnecessary delays in making medicines available for patients needs to be avoided. A reimbursement pathway with clear expectations for both parties in the negotiation would considerably reduce the ambiguity and uncertainty regarding the listing process and would considerably accelerate access to new life-saving products. Another option worth exploring to ensure rapid patient access to new medicines while incentivising manufacturers, is to put in place a funded early access programmes as has been done in France and Italy (France's ATU [xx], Italy's Law 648/96[xxi]) which helps speed up patient access to treatment whilst negotiations are taking place. By allowing access before HTA decisions are finalised, patient access to ODs can be accelerated.

Conclusion

Medicines for rare diseases will inevitably not be judged as cost-effectiveness if applied against conventional criteria. This may be most extreme for medicines for "very rare" diseases but nevertheless applies to all medicines for rare diseases. Whilst a separate ring-fenced budget, such as LSDP, can make sense for some medicines (particularly those focused on very rare diseases), and other medicines for rare diseases may satisfy conditions for Section 100, there is a danger that other valuable medicines would not satisfy either regime – we describe this as the "missing middle".

The DOH/PBAC should consider following current international best practice and developing a new pathway to ensure all medicines for rare diseases are available to Australian patients. This means either providing exemption from parts of the HTA process to medicines for rare diseases or introducing a form of HTA that is based on multi-decision criteria analysis that involves both patients and rare disease experts. This more flexible approach along with a clearer definition of scheme eligibility, more specific binding guidance on the reimbursement process, and better communication throughout the process, would greatly speed up negotiations and improve access to innovative treatments for rare disease patients.

Annex - Tables

Table 1: Definition of "Rare Disease" across the world

Organization	Rare Disease Definition	-/10,
Taiwan	< 1:10,000	1/10,
Russia	< 1:10,000	1/10,
Australia	< 2,000 people	1,2/10,
New Zealand	< 1:50,000	2/10,
Japan	< 50,000	4/10,
South Korea	< 20,000 people	4/10,
EMA	< 5 in 10,000	5/10,
US FDA	< 200,000	7.5/10,
Singapore	< 20,000	37/10,

Source: Taiwan's Department of Health; European Medicines Agency; US Food and Drug Administration; South Korea's Ministry of Food and Drug Safety; Japan's Ministry of Health, Labour, and Welfare, Alberta Human Services, Ontario Public Drug Programs; Australia Therapeutic Goods Administration

Table 2: A selection of new OD approved by the FDA in 2014

Product	Conditions	Estimated prevalence (/100,000)	Existing treatment	Patient sub-group
Hetlioz (tasimelteon)	Non-24-hour sleep–wake disorder	18.5	first and only treatment	"non-24"
Myalept (metreleptin)	complications of leptin deficiency	0.25	first and only treatment	generalised lipodystrophy
Vimizim (elosulfase alfa)	Mucopolysaccharidosis Type IV/ (Morquio A syndrome)	0.60	first and only treatment	-
Northera (droxidopa)	neurogenic orthostatic hypotensi (NOH)	10	limited treatment options	-
Alprolix (Coagulation Factor I)	Haemophilia B	2	yes	-
Hemangeol™ (propranolol hydrochloride)	Proliferating infantile hemangioma	< 70 cases	first and only treatment	-
Cyramza (ramucirumab)	advanced gastric cancer	11.9	first and only treatment	after prior chemo
Zykadia (ceritinib)	metastatic non-small cell lung cancer (NSCLC)	70	yes	ALK-positive
Sylvant (siltuximab)	Multicentric Castleman's disease	< 1	yes	HIV- , HHV-8 -
Eloctate [antihemophilic facto	Haemophilia A	7	yes	-
Ruconest (C1 esterase inhibit	hereditary angioedema (HAE)	2	yes	acute HAE attacks in adults
Beleodaq (belinostat)	patients with relapsed or refractory PTCL	2	yes	-
Cerdelga (eliglustat)	Gaucher Disease	1	yes	Type 1 form of GD

Source: OptumRx - Drug Approvals

Endnotes

[i] The innovative nature of the company is reflected in it receiving three breakthrough designations by the US's FDA for its products in cystic fibrosis. Breakthrough designation means that "preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development." http://orphandruganaut.wordpress.com/2014/01/30/fda-breakthrough-therapy-designation-vertex-pharmaceuticals-gets-31/

[ii] England, Scotland, Northern Ireland, Wales, the Republic of Ireland, France, Germany, Italy, the Netherlands, Austria, Denmark, Sweden, Norway, Greece and the United States of America

[iii] The first criteria of the LSDP is that "There is a rare but clinically definable disease for which the drug is regarded as a proven therapeutic modality, i.e. approved for that indication by the Therapeutic Goods Administration."

[iv] http://www.pbs.gov.au/info/reviews/life-saving-drugs

[v] EURORDIS (2009), "Orphan drugs: rising to the challenge to ensure a better future for 30 million patients in Europe".

[vi] Drugs for Rare Diseases: Evolving Trends in Regulatory and Health Technology Assessment Perspectives

[vii] Even though NICE's high specialised technologies (HST) process only evaluates drugs for "very rare" conditions, the prevalence rates are not defined in the published interim process NICE (2013), "Interim process and methods of the Highly Specialised Technologies Programme". This omission of using "ultra-rare" language suggests that the HST process is reluctant be associated with the prevalence rates defined for ultra-rare drugs in AGNSS, even as it builds on work done by AGNSS and NICE's 2004 exploratory work on "ultra-orphan drugs".

[viii] Hughes-Wilson, W., et al (2012). Paying for the Orphan Drug System: break or bend? Is it time for a new evaluation system for payers in Europe to take account of new rare disease treatments. Orphanet J Rare Dis, 7(1), 74.

[ix] FDA (2014), "FDA orphan drug designation 101"; EURORDIS (2009), "Orphan drugs: rising to the challenge to ensure a better future for 30 million patients in Europe".

[x] Global Genes Project, "RARE diseases: facts and statistics", https://globalgenes.org/rare-diseases-facts-statistics/.

[xi] In 2013/14 the Rare Conditions Medicines Fund supported the cost of 45 different medicines benefitting more than 200 patients. http://news.scotland.gov.uk/News/-40m-for-new-medicines-10e4.aspx

[xii] A Patient and Clinician Engagement (PACE) group was introduced in May 2014 as a way for patients and clinicians to have a stronger voice in orphan (5 in 10,000) and ultra-orphan (1 in 50,000) medicine assessments. SMC considers "modifiers" in the HTA process that allows for higher uncertainty and cost per QALY. Indeed, the announcement of the New Medicines Fund described how this should "complement changes to the way the Scottish Medicines Consortium (SMC)" to ensure patients had access to medicines for rare diseases.

[xiii] EuropaBio (2014), "Outcomes of the questionnaire on HTA and market access practices to ODs".

[xiv] In England, NICE recommendations on the use of highly specialised technologies are made by an independent advisory committee called the Highly Specialised Technologies Evaluation Committee which builds on the work of AGNSS, using multi-criteria decision analysis (MCDA)

[xv] "The Australian process for subsidised access to orphan drugs for rare inherited disorders of metabolism" April 2013, Vol. 1, No. 4 , Pages 273-277 (doi:10.1517/21678707.2013.772895) Read More: http://informahealthcare.com/doi/abs/10.1517/21678707.2013.772895http://informahealthcare.com/doi/abs/10.1517/21678707.2013.772895

[xvi] Orphan medicines have always been funded by the LSDP, Section 100 and state level funding. For example, in 2001, of the seventeen orphan medications that had marketing approval, seven had public funding. Two were listed in the Section 100 of the PBS, one was supported under the lifesaving medication program and the final four were funded on a 50:50 basis by the Commonwealth and the States/Territories. http://ses.library.usyd.edu.au/bitstream/2123/1008/2/02whole.pdf

[xvii] SMC (2014), "PACE (Patient & clinician engagement) overview document"

[xviii] Charlton L (2011) The Life Saving Drugs Program: What it means to consumers – Consumer Health Forum of Australia

[xix] Charlton L (2011) The Life Saving Drugs Program: What it means to consumers – Consumer Health Forum of Australia

[xx] France's ATU allows access to safe, pre-marketing authorisation treatments that help treat or diagnose "serious" or "rare diseases" for which there is no adequate alternative treatment. This means Patients are able to access ATU medicines 3 years faster than medicines that are not on the ATU system.

[xxi] Italy's Law 648/96 allows access to innovative treatments which have been authorised abroad but not in Italy, medicines that have undergone clinical trials but are awaiting market authorisation, and off-label use of medicines.