Submission from uniQure Biopharma B.V to the LSDP Review

uniQure would like to thank the Commonwealth Department of Health and Ageing for the opportunity to submit this document as part of the public consultation on the Post-market Review of the Life Savings Drugs Program (LSDP).

The goals of this review, as we understand them, include consideration of access and equity, value for money, and the future administration of the program. uniQure also recognises that as the LSDP grows, it is important to have a sustainable program that can accommodate new medicines.

The LSDP program plays a critical role in funding treatments for patients today, particularly for therapies for orphan and other rare diseases. Many patients would be unable to afford their medications without this program, as their therapies often fail traditional HTA cost-effectiveness criteria, due to the extremely small numbers of patients and high cost of bringing the therapies to market.

uniQure supports the development of specific criteria to fund life-saving treatments that continues to allow Australians to access innovative medicines. We also believe this fund should apply to both established and emerging therapies.

Introduction to uniQure, Glybera and LPLD

uniQure is a leader in the field of gene therapy and has developed the first and currently the only gene therapy product to receive regulatory approval in the European Union. Gene therapy offers the prospect of long-term and potentially curative benefit to patients with genetic or acquired diseases by directing the expression of a therapeutic protein or restoring the expression of a missing protein through a single administration. As a consequence of this single administration, gene therapy is unlike any of the therapies currently subsidised through the LSDP, which require ongoing treatment over the course of the patient's lifetime.

In 2012, uniQure received regulatory approval by the European Medical Agency (EMA) for Glybera (alipogene tiparvovec). Glybera is indicated for the treatment of adult patients diagnosed with familial liposomal lipase deficiency (LPLD) confirmed by genetic testing and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions. (EMA approved SmPC).

In the European Union, uniQure has been granted orphan drug exclusivity for Glybera for treatment of LPLD until October 2022, subject to the conditions applicable to orphan drug exclusivity. In Australia, uniQure is in the process of selecting a partner to represent the company and intends to apply for orphan drug designation and submit a marketing authorisation application in 2015.

Lipoprotein lipase (LPL) deficiency, LPLD, is a rare autosomal recessive inherited condition caused by homozygosity or compound heterozygosity for loss-of-function mutations in the LPL gene. LPL is primarily expressed in parenchymal cells including adipocytes, skeletal muscle cells, and cardiac muscle cells. In the fed state, LPL mainly hydrolyses triglycerides transported by chylomicrons (CM) derived from dietary sources. After eating, CM levels in the blood increase; normal LPL activity typically lowers the CM levels within a few hours after meal consumption. LPL deficiency results in severe chylomicronemia (the buildup of CM levels in the blood). LPL deficient patients suffer from a wide range of serious disease manifestations whose severity is proportional to the degree of chylomicronemia. The most severe manifestation of LPLD is pancreatitis. In daily life, LPLD patients experience recurrent and chronic abdominal pain(often starting during the childhood years), eruptive xanthomas, or depositions of yellowish cholesterol-rich material in the skin, and neurological manifestations, which include headache, itching, tingling and burning sensations, and may include memory loss.

Pancreatitis in an LPL deficiency patient often leads to admission to hospitals and/or intensive care units.

The most severe cases of acute pancreatitis are associated with an increased risk of death when infections and/or necrosis occurs. Chronic pancreatitis may also lead to pancreatic insufficiency (which is an inability to properly digest food due to a lack of digestive enzymes made by the pancreas). Pancreatic insufficiency can result in increased risk of glucose intolerance and diabetes

mellitus. In addition, as a consequence of impaired fatty acid metabolism and signalling, insulin resistance or frank type II diabetes may occur. .

Women with LPLD experience additional complications. During pregnancy, natural increases in triglycerides may increase the risk of pancreatitis, which can put both the mother and the unborn child at considerable risk. Extreme dietary fat restriction to less than two grams per day during the second and third trimester with close monitoring of plasma triglyceride concentration may be required. Breastfeeding may not be possible beyond the first few days since the breast milk is unlikely to be nutritionally complete. The likelihood of gestational diabetes is increased in LPLD mothers. Furthermore, oral birth control and hormone replacement therapy are not advised since estrogen can cause dramatic increases in plasma triglycerides, which may lead to pancreatitis.

Glybera is a gene therapy that is designed to restore the LPL enzyme activity required by tissues of the body to clear, or process, the fat-carrying chylomicron particles that are formed in the intestine and transported via the blood to the muscle after a fat-containing meal. The product consists of an engineered copy of the human LPL gene packaged in a non-replicating AAV1 vector together with promoters that allow tissue-specific gene expression. AAV1 has a particular affinity, or tropism, for muscle cells.

Prior to Glybera, there was no approved therapy for the treatment of LPLD. Clinicians advise LPLD patients to adhere to a strict diet restricting fat to less than 20% of daily calorie intake and to abstain from alcohol and medications that cause increase in triglyceride levels. Compliance with this dietary regimen is very difficult. Even with good compliance, the regimen is often ineffective in reducing chylomicronemia. LPLD patients therefore remain at increased risk for potentially lethal pancreatitis. These restrictions, as well as the need for frequent hospitalizations and the constant fear of encountering pancreatitis attacks, have a significant negative impact on the daily activity level of LPLD patients and on their quality of life. The overall mortality risk associated with an episode of acute pancreatitis is approximately 5%, it increases to 17% for necrotising pancreatitis and to 30% in those with infected necrosis.(Bruno 2010)

LPLD is an ultra-rare disease. The medical literature generally states that the prevalence of LPLD is approximately one person per million people. However, we believe that this number was not based on an epidemiological study, but rather was simply an estimate based on a non-systematic review of individual published case reports of patients with the disease and that the true prevalence may be higher, at one to 4 persons per million. Historically, physicians have not routinely tested patients for LPLD as there was no reason to do so in light of the absence of any treatment options.

LPLD patients included in the approved indication for Glybera are a subset of the entire LPLD population. In Australia we would therefore estimate there to be between 23 and 46 patients of which approximately 30% may be eligible for Glybera based on the EMA approved indication for adults, who also express >5% of the defective LPL protein. Glybera is therefore a truly personalised therapy and the LPLD patient population eligible for Glybera is by definition at high risk of incurring repeated acute pancreatitis episodes.

Glybera – summary of clinical benefits

Glybera is the only effective and approved therapy addressing the underlying cause of LPLD and has proved effective in reducing the severity of the disease and preventing its complications.

Glybera can significantly reduce the incidence of acute pancreatitis episodes in high risk LPLD patients. No patient treated as per the label had an episode of severe acute pancreatitis following Glybera administration. As a consequence of repeated acute pancreatitis episodes, LPLD patients included in the approved indication for Glybera are at particularly high risk of developing chronic pancreatitis and/or pancreatic insufficiency. In the longer term, as a consequence of chronic high lipid levels, LPLD patients covered by the approved indication for Glybera are also at risk of developing type II diabetes.

Currently, LPLD can be managed only to a certain extent and in a subset of the overall patient pool, with extremely severe dietary restrictions. In patient candidates for Glybera, control of dietary fat intake actually translates into controlling the quantity of fat consumed in each individual meal, and just one single exception to the diet may trigger an acute pancreatitis episode

The most severe LPLD patients may need to be treated with plasmapheresis. In LPLD patients candidate for Glybera, chronic plasmapheresis can be performed every four weeks or more frequently, according to the judgment of the individual physician. Plasmapheresis is an expensive procedure and is likely to negatively affect quality of life of patients in a similar way to chronic hemodialysis

Table 1. Summary of Clinical Trials with alipogene tiparvovec

Clinical studies / gene therapy tested			
Study	**Country**	**No. of Subjects**	**Intervention**
CT-AMT-011-01 + LTFU 5 years	Canada	14	Alipogene tiparvovec
CT-AMT-011-02 + LTFU (EXT) 1 year	Canada	5	Alipogene tiparvovec
Clinical records review studies			
CT-AMT-011-03	Canada	22 (17 treated, 5 untreated)	Alipogene tiparvovec
C CT-AMT-011-05	Canada/The Netherlands	29 (24 treated, 5 untreated)	AMT-010 (n = 5) Alipogene tiparvovec (n = 19)

[a] $AAV1\text{-}LPL^{S447X}$, produced using plasmid based manufacturing
[b] $AAV1\text{-}LPL^{S447X}$, produced using baculovirus based manufacturing (= marketed product in the EU, alipogene tiparvovec; Glybera®)
LPL = Lipoprotein lipase; LTFU = Long-term follow-up; EXT = Extension

After a single administration of Glybera has demonstrated long term expression of the LPL protein in injected muscles (tested up to 52 weeks post-treatment) and a sustained shift in TG-rich lipoproteins from larger particle size (chylomicrons) to smaller ones, which are less likely to trigger acute pancreatitis episodes (studies CT-AMT-11-01 and CT-AMT-11-02).

Glybera also showed a significant and sustained (52 weeks) improvement in the metabolism of large, newly-formed chylomicrons formed after ingestion of a test meal (study CT-AMT- 011-02). During an equal time period of up to 6 years pre and post-treatment, the number of events classified as "documented pancreatitis" that occurred post-treatment was reduced by 42%. Similarly, during an equal time period of up to 6 years pre and post-treatment, the number of "abdominal pain events consistent with pancreatitis" that occurred post-treatment was reduced by 52% (study CT-AMT-011-05). The lower number of pancreatitis events resulted in an approximately 50% reduction of hospitalisation days for "documented pancreatitis" over an equal time period of pre- and post-treatment follow up. For "abdominal pain events consistent with pancreatitis", there was a slight decrease in the overall number of hospitalisation days.

Table 2. Hospitalisation rates for all subjects treated with alipogene tiparvovec. Equal period of pre- and post-treatment follow up (up to 6 years)

"Documented pancreatitis"								
Subjects	**Pre-treatment**				**Post-treatment**			
	Events	Rate (event/y)	Total days	Days per year	Events	Rate (event/y)	Total days	Days per year
19	19	0.21	143	1.56	10	0.11	75	0.82
"Abdominal pain events consistent with pancreatitis"								
Subjects	**Pre-treatment**				**Post-treatment**			
	Events	Rate (event/y)	Total days	Days per year	Events	Rate (event/y)	Total days	Days per year
19	18	0.20	116	1.27	11	0.12	107	1.17

y = year

Access to Orphan Medicines in Australia:

In order for patients to have timely access to orphan medicines it is necessary to have both a regulatory and reimbursement framework that can accommodate these unique products and the specific needs of patients with rare diseases.

uniQure congratulates the TGA on the announcement for a strengthened collaboration for orphan medicines with the EMA. We note the two regulators have agreed to share the full assessment reports related to marketing authorisations of orphan medicines, which are intended to treat rare diseases. The TGA has stated the following:

"this agreement will contribute to accelerating access to new medicines for patients with rare diseases in Europe and in Australia. Global collaboration on orphan medicines and rare diseases is particularly important in view of the small number of patients worldwide and the need for the limited number of studies performed to benefit patients regardless of where they live."

http://www.tga.gov.au/media-release/ema-and-australian-regulatory-authority-strengthen-collaboration-area-orphan-medicines

uniQure supports this statement but believes the objective of accelerating access to new medicines for patients of rare diseases will not be met unless there is a clear reimbursement framework. This is especially true for rare diseases where prices for many new medicines would constitute an unreasonable financial burden for the patient or their family.

The LSDP currently provides a mechanism for funding new medicines for rare and life threatening diseases. uniQure supports maintaining a separate funding mechanism for rare and ultra-rare diseases.

We understand that under section 100A of the National Health Act 1953, a medicine can only be added to the Pharmaceutical Benefits Scheme if the Pharmaceutical Benefits Advisory Committee makes a positive recommendation to the Minister for Health. We also understand that the PBAC can only recommend a medicine for listing on the PBS if it is safe, effective and cost effective. We are not aware of any formal definition of "cost effectiveness".

It is widely accepted that medicines for ultra-rare diseases are often not cost effective according to conventional HTA cost-effectiveness criteria. uniQure would therefore be concerned that if a specific funding mechanism like the LSDP were not maintained in Australia, patients with ultra-rare diseases may be denied access to innovative life saving medicines.

uniQure believes that Glybera should be considered as an emerging clinical treatment in the context of the Post market review of the LSDP and that the LSDP would be the appropriate program for evaluating a reimbursement application. Glybera and LPLD meet the current criteria for the LSDP.

Finally, as Glybera is indicated for patients with LPLD confirmed by genetic testing, it is important that there is also reimbursement for and access to the relevant genetic test so appropriate patients can be identified and gain access to treatment.

The future for Gene Therapy and other innovative medicines.

Australians need the LSDP to access beneficial and potentially curative treatments that are available internationally. A single treatment by gene therapy can improve the lives of Australians suffering from extremely rare diseases such as LPLD and also reduce the burden on their families who are currently often managing the costs of therapies and care. Gene therapy also has the potential to significantly change health care delivery if the goal of curative treatment with a single administration can be realised.

Glybera is the first of a truly innovative emerging pipeline of gene therapy based on uniQure's unique proprietary modular technology platform. It is therefore critical that gene therapy treatments are included in the scope of the LSDP so patients can benefit from these types of treatment.

uniQure supports the development of specific criteria for funding new medicines for rare and life threatening diseases that take account of emerging and new treatments, ensure a sustainable and manageable program for the future and most critically ensures that Australians will continue to benefit from access to innovative lifesaving medicines.

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