Information Paper
On
Pompe Disease In The Asia Pacific Region

11th April 2011

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EXECUTIVE SUMMARY

The purpose of this paper is to provide KKH with information on Pompe Disease and the medical support that patients have received in the Asia Pacific region. It discusses lifelong treatment that Pompe Disease patients require and how they have benefited and will continue to benefit from the only treatment available in the market now – Enzyme Replacement Therapy (ERT). Case studies have been included to illustrate how ERT has improved the quality of life for these patients. It also elaborates on the financial reimbursement and other supportive care that Pompe Disease patients have received from their Government in the region. The various forms of help and care provided in other countries can be used as a form of reference by the Healthcare ministry and other medical providers in Singapore, to formulate a comprehensive healthcare support for Pompe Disease patients here.

1 Pompe Disease

1.1 What is Pompe Disease?

Pompe Disease is a rare inherited neuromuscular disorder that causes progressive muscle weakness in people of all ages. It is estimated to have affected between 5,000 to 10,000 people worldwide. The exact number of individuals affected by this condition is hard to determine as it can be difficult to diagnose *(Ausems, Verbiest & Hermans 1999).*

Pompe Disease is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid GAA (alpha-glucosidase). In Pompe Disease, lysosomal glycogen accumulates in many tissues especially in skeletal, cardiac, and smooth muscle *(Kishnani & Howell, 2004).* The build-up of glycogen in the muscle tissues

causes progressive muscle weakness throughout the body and cardiac or respiratory complications are the main causes of death for Pompe Disease patients.

1.2 Pompe Disease Classification

Pompe Disease can be divided into three forms, namely, Infantile-onset, Juvenile-onset and Adult-onset. They are defined by age of onset and progression of symptoms. However, it is more commonly divided into two main groups: Infantile onset (involving the massive enlargement of the heart) and Late onset (no heart enlargement), which consist of juvenile and adult patients.

In infantile-onset Pompe Disease, the most severe and rapidly progressive form, patients present with hypertrophic cardiomyopathy, hepatomegaly, generalised weakness, hypotonia and death due to cardiorespiratory failure in the first year of life *(Van den Hout, 2003).*

Late onset (juvenile/adult) Pompe Disease is the result of a partial deficiency of GAA. The onset can be as early as childhood or as late as adulthood. The primary symptom is muscle weakness progressing to respiratory weakness and death from respiratory failure. The heart may be involved but it will not be grossly enlarged *(www.ipa.org).*

1.3 Pompe Disease Statistics Worldwide

Incidence data are limited with reports ranging from 1 in 14,000 to 1 in 300,000 depending on the ethnicity or the geographical area studied. The infantile form has an apparently higher incidence among African-Americans and Chinese; whereas the late-onset adult form has a higher incidence in Netherlands. In the Netherlands, the

incidence of the infantile-onset form is 1 in 183,000. The combined incidence of all forms of Pompe Disease is estimated to be 1:40,000 *(Hirschhorn & Reuser, 2001)*.

The combined incidence of all forms of Pompe Disease varies, from 1:14,000 in African Americans to 1:100,000 in individuals of European descent.

Population	**Incidence**	**Reference**
African American	1:14,000	*(Hirschhorn & Reuser, 2001)*
Netherlands	1:40,000 combined 1:138,000 infantile onset 1:57,000 adult onset	*(Ausems et al,1999, Poorthuis et al, 1999)*
US	1:40,000 combined	*(Martiniuk et al,1998)*
South China/Taiwan	1:50,000	*(Lin et al,1987)*
European descent	1:100,000 infantile onset 1:60,000 late onset	*(Martiniuk et al,1998)*
Australia	1:145,000	*(Meikle et al,1999)*
Portugal	1:600,000	*(Pinto et al,2004)*

In 1999, Frank Martiniuk reported the results for testing 3,000 newborns for 3 different mutations common in that population. Based on the carrier frequency derived, the estimated incidence for Infantile-onset Pompe Disease is 1 in 536,000 *(Martiniuk, 1999).*

1.4 Pompe Disease Treatment

The only treatment available currently, for Pompe Disease patients, is a process called Enzyme Replacement Therapy (ERT), where they are administered with an enzyme called Myozyme (alglucosidase alfa). It has shown, in clinical trials with infantile-onset patients, to decrease heart size, maintain normal heart function, improve muscle function, tone, and strength, and reduce glycogen accumulation *(Klinge, Straub & Neudorf*, *2005).* Myozyme is administered by intravenous (IV) infusion. This is a

process that involves injecting the drug into a vein, directly into the bloodstream. The total volume of infusion is determined by the patient's body weight and should be administered over approximately 4 hours. Myozyme should be administered by a healthcare professional and patients must be monitor during the course and even the 2 hours that follow, in case of allergies or any other possible reactions to the treatment.

Myozyme is the first specific treatment for Pompe Disease. Myozyme has been shown to improve ventilator-free survival in patients with infantile-onset Pompe disease as compared to an untreated historical control, whereas use of Myozyme in patients with other forms of Pompe disease has not been adequately studied to assure safety and efficacy.

The movie “Extraordinary Measures”, based on the true story centered on the efforts of John and Aileen Crowley to find a researcher who might have a cure for their two children diagnosed with Pompe Disease. In 2003, their children, Megan and Patrick were able to begin a three-year clinical trial of a drug for Pompe, discovered and produced by Genzyme through the efforts of John and hundreds of other people. Since May, 2006, they have been treated with the commercially approved drug, Myozyme, and continue to be healthy because Myoyzme is keeping their body system stable.

1.5 Patients Care and Treatment

The effects of Pompe Disease can vary widely from person to person; therefore, care and treatment plans must be individualized to each patient's needs. Moreover, because the Disease is always progressive and it will worsen over time, regular follow-up is important to check on the Disease progression and adjust patient's care as needed *(Kishnani, Steiner & Bali, 2006).*

Managing symptoms of Pompe Disease includes supportive care to help with movement, breathing difficulties, and other symptoms. Pompe Disease management requires a comprehensive team approach from a variety of health care providers.

A multidisciplinary care team is usually required by the patient, including neuromuscular specialists, metabolic specialists, pulmonologists, cardiologists, physical therapists and speech therapists. The hospital plays an important role in educating and offering encouragement to the patients and their family members. Specialists should maintain regular communication with the patients, their family members and caregivers. A "Care coordinator" should be appointed, to plan and look into the required care and support holistically.

2 Pompe Patients Profile

The following patients are featured to illustrate the amazing effect of Myozyme and how this enzyme has prolonged and changed the quality of their life, while they wait for a cure to be found.

2.1 Megan Assink (USA)

Megan was one of the first children in the world to be enrolled in clinical trials for Myozyme (alglucosidase alfa), then an experimental treatment for Pompe Disease. Megan was the second child in her family diagnosed with the rare genetic Disease. Her older sister Kelsey died at age nine from the progression of Pompe Disease. Shortly after Kelsey's death, Megan, still an infant was diagnosed with the same Disease that claimed her sister's life. As with Kelsey, there were no treatments available for Megan at the time.

In the year following her diagnosis, Megan developed cardiac and respiratory problems and showed signs of delayed development, including difficulty crawling, sitting and standing up. Doctors predicted Megan would spend most of her life in a wheelchair and on a ventilator like her sister Kelsey.

But Megan was fortunate. Megan's parents found out about a clinical trial for Myozyme, then an experimental enzyme replacement therapy, which had begun at a few hospitals around the world. Megan participated in the clinical trial and she gradually began to gain trunk strength and was able to pull herself up to a standing position on her own. Within a year, Megan was able to walk without any support.

Today, at age five, Megan is an active little girl who loves to play with her sister and brother, Hope and Tyler. She continues to receive an infusion every two

weeks, which is supplemented by physical, occupational and speech therapy. Her echocardiogram results, a test to assess whether heart muscle has become too thick, show her heart as normal. “We are amazed and truly blessed by her progress,” says her father, Greg Assink.

2.2 Yen Ling and Wei Ling (Malaysia)

Yen Ling and Wei Ling are sisters from Malaysia who were diagnosed with Pompe Disease in 2005. The family has three children and their second child, a boy named Sze Hong, was free from the disease.

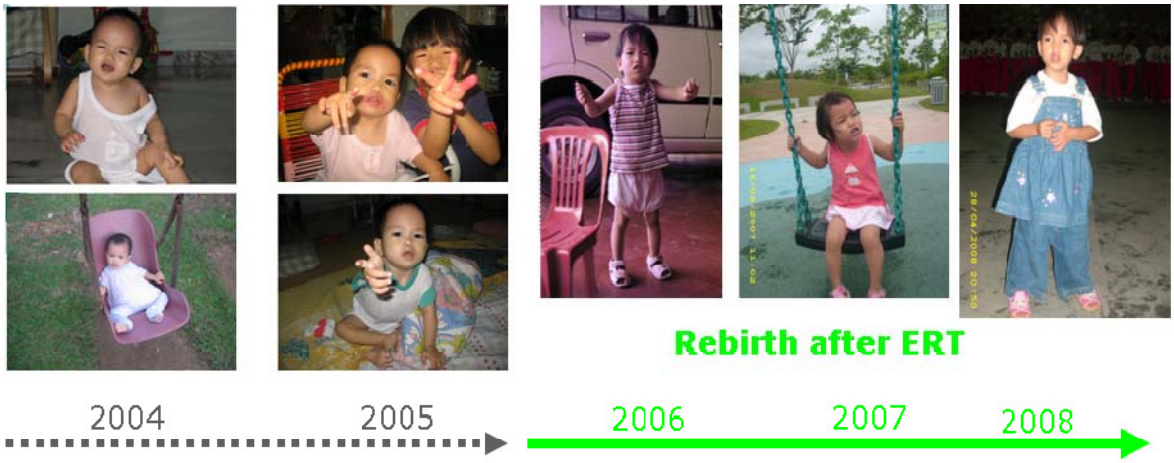
Yen Ling started showing muscle weakness when she was 2 years old. However, her parent did not seek for medical advice until she was 3 years old when she developed severe lower limb weakness problem. Although she underwent several months of occupational therapy to improve her muscle strength and motor skill, her condition did not improve. Wei Ling was born during this period and during her early months; she fell sick easily but would recover within a week. Although she had delayed development, her parent thought that it was due to her poor health condition. Wei Ling’s health got worst and she was suffering from respiratory infection for almost 2 months before she

was finally admitted to the hospital. Both sisters were found to have enlarged heart and the pediatric cardiologist then immediately referred them to geneticists in Hospital Kuala Lumpur and this was the first time the family heard of Pompe Disease.

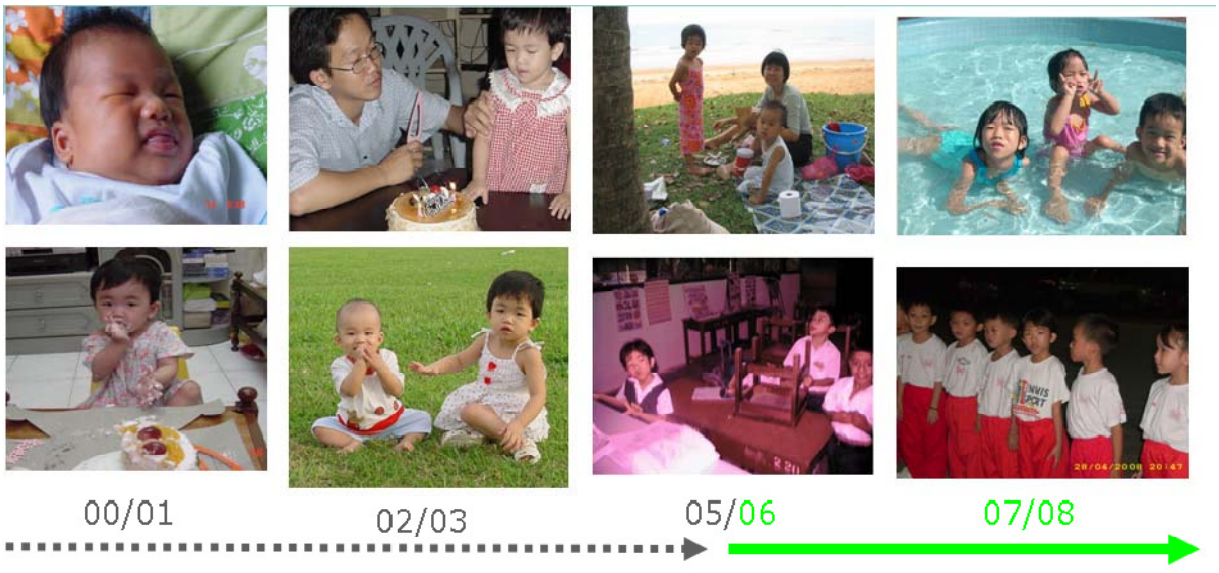
After 3 weeks of investigation and 2 months of waiting, Yen Ling and Wei Ling were confirmed to have Pompe Disease. This was when they first heard of a miracle drug Myozyme which might save the girls' life. In April 2006, after waiting and fighting (to get the legal document to import an unregistered drug into Malaysia) for months, the sisters received their first ERT infusion. It did not take long for the family to notice the drug was working well on the girls. Wei Ling started to smile easily and after 2 months of treatment, she started to acquire new motor skill. Wei Ling started to hold on things to stand up and after 8 months of ERT, she started to walk without support. It was the most beautiful moment of her life that she was given a second chance to live on.

While Wei Ling was making good progress, Yen Ling also showed to have improved strength on her lower limbs after ERT infusion. She could start to up the stairs without support which was impossible before her treatment. With Myozyme infusion, both sisters have improved in their hearing ability and both their heart and liver have strunk to normal size. Wei Ling has showed improved EF especially and that might explain her higher mobility and energy level.

"Myozyme is such a wonderful gift for our girls. Without it, we could not imagine how would they be now or if they are still around. We pray every day that our Malaysia Government will continue to fund their medical fee as long as they need it. We hope more Pompes in Malaysia could be saved by Myozyme" says their father, Lee Yee Seng.



Wei Ling survival proved nothing is impossible in this world. Determination, perseverance, compassion, gratitude are the key success in our daily life.



Myozyme has freed Yen Ling from tracheotomy, wheelchair bound as normally happen to Pompe patients. Now she can pursue her education and she hopes to represent the school for Kung Fu martial art one day!

2.3 Chloe Mah (Singapore) 

Chloe was born in November 2009 and all were well until when she was more than five months old. She presented signs of delayed development and low muscle tone. Chloe was being referred to specialists at KK Hospital who dealt with growth hormones program, neuro-muscular and genetics disorders.

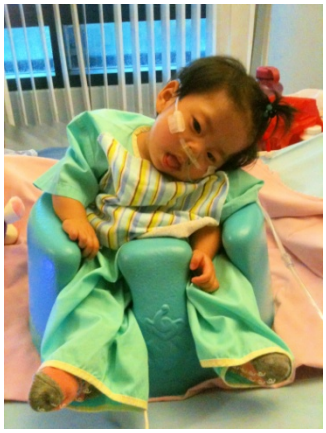
Meanwhile, little Chloe fell ill suddenly and her condition persisted for more than a week, despite consulting several pediatricians and putting her on various medications. She was admitted to KKH in June 2010 for bronchitis. Upon admission, the doctors discovered that she has a 'big heart' (cardiomyopathy). On 2nd July 2010, 2 weeks after admission and under intensive care, Chloe was confirmed to be suffering from a very rare genetic condition – Pompe Disease.

The family was presented with the hard fact that she had only 2-3 months to live. Based on past research, two thirds of those who undergo treatment might survive. Amongst those who survive, only half of them could lead a 'normal' life – having the ability to walk, feed and do without respiratory support. To add to these, the family was informed that medical cost of the ERT would be a hefty sum of up to $300,000 per year (and increasing as she grows older and requires higher dosage), not including cost of hospitalization and other supplementary care and medication.

The parents could not bear to give up her life at such a tender age, despite all the uncertainties and pessimistic information presented. No one should have the right to deny her the chance to live. Chloe received her first ERT in August, 2010. Six months through her treatment, Chloe's condition improved tremendously, with a significant reduction in the size of her heart. She was able to hold herself up in a sitting position without support and her neck and trunk control were also much better, relative to her

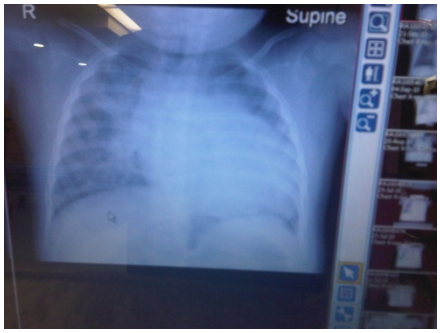
pre-treatment stage. Her reliance on Bi-PAP was reduced. It was no longer needed around the clock but only during her sleep. Besides improvements in her muscle strength, Chloe is capable of communicating with people by gesturing and making specific sounds. She even learnt to play many games and use various applications to listen to songs and stories on iPad!

Like other Pompe Disease patients, Chloe has to go for her ERT every fortnightly. Her supportive care includes regular physio, speech, occupational, nutritional and respiratory therapies. Her doctors and therapists are looking forward to her reaching the next milestone, where she will hold herself up on standing position and start walking.

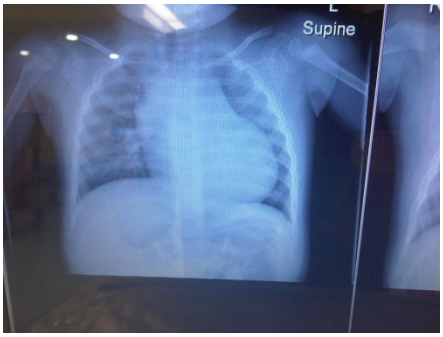


July, 2010. On the day Chloe was Diagnosed with Pompe Disease.

March, 2011. After her 16th ERT, Chloe is able to hold herself in a sitting position without support. She has regained her neck muscle control as well.



June, 2010. X-ray showed Chloe Is suffering from Cardiomyopathy



Jan 2011 Significant reduction in the size of her heart.

3 Myozyme Reimbursement in Asia-Pacific Region

Myozyme, a man-made lysosomal glycogen-specific enzyme, has received market approval in a growing number of countries. Since the approval by FDA in 2006 for Myozyme to be used for Pompe Disease treatment, as of March 2010, 44 Countries have approved Myozyme reimbursement or approved insurance coverage *(Appendix 1)*.

Among the 44 countries that approved funding for Myozyme, there are several countries from the Asia-Pacific region:

- **Hong Kong**
- **Taiwan**
- **Malaysia**
- **Korea**
- **Japan**
- **Australia**

3.1 Medical Scheme in Hong Kong 

The Department of Health (DOH) is responsible for health legislation and policy in Hong Kong. The DOH is made up of a number of smaller divisions, including the Medical Device Control Office, Center for Health Protection, Dental Service, Radiation Health Unit, and Pharmaceutical Service. The Pharmaceutical Service is responsible for drug registration and drug import/export control in Hong Kong.

In December, 2008 the Hong Kong Hospital Authority (HA) Expert Panel on Rare Metabolic Diseases met to discuss and deliberated on the treatment modality of two brothers with Pompe Disease. The meeting arrived at a unanimous decision that both

patients were suitable for Enzyme Replacement Therapy *(Hong Kong Hospital Authority, 2010).*

According to the press release, HA had also been given additional funding for drugs by the Government (for Year 2010-11), part of which would be allocated to the spending on ERT for six types of rare metabolic Diseases including Mucopolysaccharidoses I, II and VI, Pompe Disease, Fabry Disease, and Gaucher Disease. All the Diseases were classified under the Lysosomal Storage Disease "umbrella" *(Appendix 2).*

The additional funding was said to be amounting to $10 million and it was for the purpose of providing ERT to patients with rare genetic lysosomal storage diseases *(http://www.hk-mps.com/en/index.html).*

The rally for Government funding was initiated by the patients' support group, which acted as a source of pressure for the healthcare ministry. Numerous and persistent dialogue sessions were held during between them during this intense period. With full funding from the HA, patients with rare conditions had a better chance of prolonging their life span and improving their quality of life.

3.2 Medical Scheme in Taiwan 

Taiwan was one of the very first countries in Asia to fund and support patients with Rare Diseases. In January 2000, after 3 readings in the Legislative Yuan, the President announced the enactment of the Rare Disease and Orphan Drug Act. The Rare Disease and Orphan Drug Act enacted in 2000 in Taiwan covers a broad spectrum of needs, including a subsidy for expenses not covered by the National Health Insurance,

increased public education awareness and education, and licensing a genetic consultation network. Henceforth, patients with rare Disease were heavily subsidized for their medical care and treatment. They could apply for reimbursement of medical expenses that included diagnosis, treatment, drugs, and special nutritional supplements. The reimbursement was capped at 70% of actual expenses. However, patient in families that qualified for low-income status could receive reimbursements up to 100% for drugs and nutritional supplements *(Taiwan Foundation for Rare Disorders, 2004)*.

It all began in 1998 when parents of 2 separate rare disease patients worked together to promote the systematization and legalization of rare disease issues in Taiwan. With the persistence of the rare disease support group and tremendous support from the society, Taiwan Foundation for Rare Disorders (TFRD) was formally established in June 1999. TFRD set off their rally for the adoption of the "Rare Disease Control and Orphan Drug Act", with emphasis on fundamental rights and benefits for rare disease patients .

There used to be 3 different versions of the “Rare Disease Control and Orphan Drug Act” drafted by The Bureau of Pharmaceutical, the Legislation Yuan and TFRD. The 3 parties finally consolidated the whole spectrum of laws into one Act that contained 36 articles, detailing resources from all levels towards the prevention and treatment of rare diseases *(Appendix 2).*

Rare disease patients can now apply for reimbursement of the medical expenses incurred, through their doctors or medical institutions. Patients who have been officially

acknowledged as suffering from rare diseases, can apply for reimbursement of such medical expenses occurred in local medical centers, or regional teaching hospitals.

3.3 Medical Scheme in Malaysia 

The rally for medical support from the Malaysian government started with the patients' group's collective effort. Medical doctors were roped in along the way, to render support to the cause (as with all other societies). It started with dialogues with relevant parties including officials from the Ministry Of Health and politicians, which ultimately led to the funding proposal being tabled at cabinet meetings, and finally approved by the government for the funding of ERT. The funding scheme in Malaysia had started 4 years ago (2006) and adopted the 'capped' funding model. Some patients had to wait in line for funds to be available. At present, there are 6 Pompe Disease patients in Malaysia receiving regular ERT and enjoying full funding from the Government.

When a new patient is diagnosed with the Disease, his/her case will be presented to a committee, consisting of medical doctors, which will deliberate and decide if this patient has a good chance of survival and hence ought to be treated. Such decisions are based on a set of Guidelines drawn out (when the committee was formed). After the committee gives the green light to proceed with the treatment, based on medical merit, it will then be dependent on whether such budget is available to fund the treatment for the said patient. If no funds are available, the patient will be put on the waiting list until new funds are made available.

3.4 Medical Scheme in Korea 

The Korean National Institute of Health includes within its structure an Orphan Drug Center, a Genetic and Rare Disease Center, and a Department of Biomedical Sciences that is committed to increasing research on rare diseases. As in Taiwan, there is an active patient community in Korea, organised by the Korean Organization for Rare Diseases (KORD) (*http://www.pharmafocusasia.com).*

In 2001, the Korean Ministry of Health and Welfare started their support for 4 types of rare disease through the Medical Aid Program and the National Health Insurance for low-income subscribers. The number of diseases supported by the program had grown over the years and as at 2010, a total of 132 diseases were drafted into the medical fee supported by the project *(http://english.mohw.go.kr/front_eng/index.jsp).*

Under the program, patients with rare diseases could apply for funding of the following expenditures through public health center:

- Statutory out-of-pocket health expenditures among medical benefits for treatment of rare/incurable diseases and their complications
- Patients suffering from muscular dystrophy, multiple sclerosis, hereditary ataxia, mucopolysaccharidosis, or adrenoleukodystrophy

    - Costs for the purchase of assistive devices

    - Rental fees for respiratory apparatuses (up to 800,000 won per month)

    - Support for care expenses (300,000 won per month; only for patients with grade 1 physical disability or grade 1 brain lesions).

The centerpiece of this structure was the National Health Insurance, governed by National Health Insurance Act. Every Korea citizen residing in Korea (and a few others) was automatically enrolled in the health insurance. The only exception was those who received “medical protection”. “Medical protection” was an out-and-out

welfare system, where all medical expenses were paid for and the beneficiary did not need to pay any premium for this coverage. This was reserved for the extremely poor, refugees, children of independence fighters and other significant contributors to Korea, possessors of important intangible cultural products and so on *(http://askakorean.blogspot.com/)*.

3.5 Medical Scheme in Japan 

In Japan, the Specified Disease Treatment Research Program subsidizes medical care for patients of rare and intractable diseases. Although 30% co-payment is required for insurance-covered medical care in most cases, the national government and prefectures partly cover the patients' share of medical expenses through this program. Currently, Pompe Disease patients are reimbursed by Government in Japan under the Specified Disease Treatment (Tokutei Shikkan) Program and these patients pay between US Dollars 100 - 200 per month *(http://www.nanbyou.or.jp/english).*

The Japanese phrase "tokutei shikkan" literally means "specified diseases." Treatment of these designated diseases is very expensive, carrying a high cost of long-term care and medicine. This causes great financial and mental stress on the patient's family. Due to the lack of information and statistics about the cases of these rare and intractable diseases, a nationwide study on such diseases is needed. Currently, this system applies to 56 intractable diseases and it includes Lysosomal Storage Disease. Recent orphan drugs approved in Japan include Glaxo's Lexiva for HIV infection, Genzyme's Fabrazyme for Fabry disease, and Novartis's Visudyen for age-related macular degeneration.

The subsidy for the treatment of a specific disease is on a yearly renewal basis, normally effective from October 1 of the current year to September 30 of the following year. However, the subsidy for the treatment of fulminant hepatitis or severe acute pancreatitis is valid for six months only.

Recipients of Specified Disease Treatment with the following conditions receive subsidy for all the medical cost of their specified disease.

- Lower-income recipients who are exempted from resident tax
- Patients with severe conditions due to diseases approved by the prefecture
- Patients with sub-acute myeloopticoneuropathy, prion diseases, fulminant hepatitis, or severe acute pancreatitis

Other recipients are subjected to copayment, as required by the public health insurance policy at the medical institution, in accordance to the table below:

Types of Patients	Limits to Monthly Shares by Types of Patients		
	Hospitalization	Outpatient Care	If the patient supports his or her own living
The person supporting the patient's living is exempt from resident tax.	¥ -	¥ -	¥ -
The person supporting the patient's living is exempt from income tax for the previous year.	¥ 4,500.00	¥ 2,250.00	Monthly limit is a half of the amount shown left for patients who supports his or her own living
The person supporting the patient's living paid income tax of 5,000 yen or less for the previous year.	¥ 6,900.00	¥ 3,450.00	
The person supporting the patient's living paid income tax of between 5,001 yen and 15,000 for the previous year.	¥ 8,500.00	¥ 4,250.00	
The person supporting the patient's living paid income tax of between 15,001 yen and 40,000 yen for the previous year.	¥ 11,000.00	¥ 5,500.00	
The person supporting the patient's living paid income tax of between 40,001 yen and 70,000 yen for the previous year.	¥ 18,700.00	¥ 9,350.00	
The person supporting the patient's living paid income tax of 70,001 yen or more for the previous year.	¥ 23,100.00	¥ 11,550.00	

3.6 Medical Scheme in Australia 

The Australian Government provides subsidy to Pompe Disease patients through the Life Saving Drugs Program. Through this program, the Government provides subsidized access, for eligible patients, to expensive and potentially lifesaving drugs for very rare life-threatening conditions. At the moment, 6 drugs that are funded under the program, on an annual basis. They are:

- Cerezyme and Zavesca for the treatment of Gaucher Disease
- Replagal and Fabrazyme for the treatment of Fabry Disease
- Aldurazyme for the treatment of MPS Type I
- Elaprase for the treatment of MPS Type II
- Naglazyme for the treatment of MPS Type VI
- Myozyme for the treatment of Infantile-onset Pompe Disease

Before a drug can be included in the Life Saving Drug Program, it must be accepted by the Pharmaceutical Benefits Advisory Committee (PBAC) as clinically necessary and effective, but not recommended for inclusion on the Pharmaceutical Benefit Scheme due to high cost.

In July 2008, the PBAC recommended that Myozyme be included on the LSDP to treat only Infantile-onset Pompe Disease. The reasons for PBAC to make such recommendation were:

- Insufficient data were presented on the clinical efficacy of Myozyme in the treatment of late-onset Pompe Disease
- Myozyme increased the patient's life expectancy, thus fulfilling the criterion 2 of the LSDP

- The drug also met criterion 1 of the LSDP where it was regarded as a proven therapeutic modality
- Pompe Disease was a rare condition where it could be identified with reasonable diagnostic precision, thus meeting criterion 3 of the LSDP

From January 2010, the Government had approved funding for Myozyme through the LSDP for Infantile-onset Pompe Disease patients who met the program condition and criteria. When the patient qualified for the subsidies through LSDP, the Government would provide financial assistance for the purchase of the drug. The purchase price of the drug would be one that was negotiated by the Commonwealth with the supplier, in accordance to the guidelines established by Pharmaceutical Benefits Pricing Authority *(Department of Health and Ageing).*

It was written in the guidelines that the estimated incremental cost per patient was in the range between $75,000 to $105,000 for ERT treatment (without supportive care cost offset). Based on the estimated birth prevalence in a published literature, which is 1:100,000 *(Martiniuk et al, 1998)*, the likely number of patients per year for Infantile-onset Pompe Disease was estimated to be up to10.6 patients in Year 5. The financial cost per year to the PBS was estimated to be less than $10 million in Year 5 for Infantile-onset Pompe Disease patients *(Appendix 4).*

3.7 Medical Scheme in Singapore

In 1990, the Government introduced MediShield to help members meet medical expenses arising from major illnesses, which could not be sufficiently covered by their Medisave (which is a form of saving account) balance. Members were advised to take

up MediShield or an appropriate private Integrated Shield Plan in order to stretch their Medisave dollars. However, this kind of low cost catastrophic illness insurance scheme did not cover patients from orphan drugs.

The Government also introduced an endowment fund called Medifund in 1993 to help needy Singaporeans who were unable to pay for their medical expenses. Medifund acted as a safety net for those who could not afford the subsidised bill charges, despite having Medisave and MediShield coverage. The Government utilized interest income from the capital sum, which stood at S$1.7 billion (FY 2009), to help needy patients who had exhausted all other means to pay their medical bills *(http://www.moh.gov.sg).*

Although the people were able to benefit from their insurance coverage and received further support from Medifund, none of the schemes covered the patients from orphan drugs which were generally very costly. There had been little mention about rare diseases in the current medical schemes introduced.

The orphan drugs policy in Singapore is based upon a Medicine Order ("Orphan drugs Exemption"). The legislation, which came into force at the end of 1991, gave a definition of orphan drugs and of the legal framework for imports in Singapore. So far, there has been no other incentive, such as marketing exclusivity or subsidies in the orphan drug policy (*http://www.pacificbridgemedical.com).*

It might suggest that more ought to be done to increase the awareness of rare diseases in Singapore and to draw attention to the small group of patients suffering

from such conditions. More attention needed to be directed to these patients, whose hefty treatment cost could only be made sustainable with government funding.

Currently, a patient who was suffering from rare disease and required financial assistance, needed to apply for such funding through the medical social worker at the hospital. The outcome of the application was dependent on the financial status of the patient's family, the medical merit of the case and the amount of funds available at the time of application. While the case was approved, it would still be subjected to quarterly review, on whether the funding would continue.

Other forms of financial support for such patients included private and public (which could only be done through a Foundation and with a license) donation and fund raising. Unfortunately, these were not long term solutions due to the lack of constant support from the general public and the Government.

At the moment, Chloe Mah is the only case of Infantile Pompe Disease in Singapore and she is currently receiving ERT at KKH.

4 Reflection

This paper provides a basic understanding of Pompe Disease and how the patient's quality of life has improved after receiving ERT. It is also evident that the government in the various countries in the Asia-Pacific region plays a significant role in helping Pompe Disease patients and their families cope with the condition and especially the financial assistance that they need in the long term.

Many developed countries in Asia set certain guidelines on orphan drugs program to help those patients with rare disorders. Through these programs, the patients are given a chance to live longer and better.

Taiwan has implemented the Rare Disease and Orphan Drugs Act to help patients with their medical expenditure. Countries like Hong Kong, Malaysia, Japan and Korea are offering extra funding to help with the medical expenses of patients with rare diseases. All these are made possible with the efforts of the patients' groups and the intervention of the Government.

Experts say it is unclear what the time horizon is that the patients will continue to require ERT, how long the benefits of ERT will last, if not as long as the patient lives, and what his/her life expectancy is going to be. The only comforting truth is that Pompe Disease patients who are administered with Myozyme through ERT and responding to it, are clearly living not only longer, but much better *(http://www.asiasmedicaltourism.com).*

ERT is not a cure for Pompe Disease but it does keep the effects of missing enzyme at bay. Pompe Disease should no longer be classified as a terminal illness but a chronic

disorder that can be managed similarly to how diabetes is managed through insulin. It is important for other countries (besides those featured here above), such as Singapore, to start looking into offering financial support and sustainable treatment for the rare disorder patients.

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Australian Government – Department of Health and Ageing
Guidelines for the treatment of Infantile-onset Pompe Disease through the Life Saving Drugs Programs

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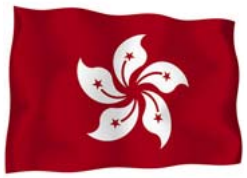
Appendix 1

As of March 2010 44 Countries have approved Myozyme reimbursement or approved insurance coverage these countries include.

	Country	Diagnosed				Treated				Reimbursement
		TOTAL	Adults	Juvenie	Infants	TOTAL	Adults	Juveniles	Infants	
1	Netherlands	113	88	18	7	101	80	14	7	Government via speciol Orphar Diseases Program
2	Germany	150	126	15	9	124	100	15	9	Health Insurance (Krankenkasse). These Health Insurances are obliged to reimburse in the situation of a rare disease without any other treatment.
3	Norway	1	1			1				Government
4	Hong Kong	3			3	3			3	Government
5	UK	120				95	14	9	72	Government
6	Italy	70				70				Local Government via the local health care system all over Italy. All patients from babies to adults receive reimbursement
7	Spain	40	20	16	4	36	16	16	4	via hospitals of Public Health System
8	Belgium	33				23				Government via what they call 'Solidarity Fund' especially for expensive drugs
9	Romania	1		1		1		1		Government
10	Turkey	18	8	7	3	13	8	7	3	The importation process is done through Pharmacist's Association (TEB) on named patent basis. The patients receive 100% reimbursement.
11	Algeria	4				4	4			Government
12	Sweden	6	5	1		5	1			Government
13	Hungary	9	8	1		7	6	1		Government on named patient basis
14	Poland	20	10	7	1	18	10	7	1	Government. 2 patients who are not treated yet are awaiting to receive refund from the national health system. Infants start immediately via ICAP and then commercial treatment
15	Czech Republic	2	1			1	1			Government
16	Malaysia	4		2	2	4		2	2	Government
17	Israel	11	1		10	11	1		10	Government
18	Austria	15	11	2	2	14	10	2	2	Insurance or Government organised insurance.
19	Slovenia	2		1	1	2		1	1	Government
20	Portugal	2	1	1		2	1	1		Government
21	Greece	16	8	5	3	14	6	5	3	Government
22	Canada	29	21	3	5	15	7	3	5	Government (organized on State basic) Two juveniles are still on ICAP because their state doesn't
23	Japan	60	10	17	3	59	10	17	3	Specified Disease Treatment (Tokutei Shikkan) program reimbursed by Government. Patients do pay 100 - 200 US Dollars per month. Its not exactly known what the distribution of the onset is.
24	Denmark	6	2	4		6	2	4		Government
25	USA	400	330		70	170	100		70	Insurance.
										As ofMarch 2010



Appendix 2

PRESS RELEASE

Hospital Authority Building, 147B, Argyle Street, Kowloon, Hong Kong
Wednesday, 8 December 2010
Attention News Editors:

The Hospital Authority (HA) Expert Panel on Rare Metabolic Diseases met today (8 December 2010) to discuss and deliberate on the treatment modality of two brothers with Pompe Disease. The meeting arrived at a unanimous decision that both patients are suitable for the use of Enzyme Replacement Therapy (ERT).

The doctor in charge has been informed to convey the Expert Panel's decision to the patients and their family. Both of them are currently receiving specialist treatment at the outpatient clinic of Princess Margaret Hospital.
Dr Luk Che-chung, Expert Panel Chairman and Cluster Chief Executive of Hong Kong West Cluster, said after the meeting that, "Expert Panel members have made the decision with reference to established clinical indicators and with due consideration given to the latest evidence-based criteria as published in the New England Journal of Medicine in April this year. While exercising their professional judgement, the experts have carefully assessed the patients' clinical condition and a balance of the risks and benefits of the treatment. I have to thank all the experts for their valuable inputs to help us assist the patients in need."

Dr Luk pointed out that the doctor in charge will explain in detail the treatment process to the two patients including the clinical risk and expected outcome. The procedure will need to be performed in the Intensive Care Unit. The clinical effectiveness and outcome will be regularly reviewed to assess the risk factor and benefits of the treatment. Adjustment of the treatment plan will be made on a need basis.

According to the experts, replacement therapy will need to be conducted together with other supportive treatment as a total package to achieve the best possible outcome, including appropriate level of exercise and dietetic therapy. Members of the Expert Panel include four senior paediatricians, a senior clinical oncologist and a senior clinical pharmacologist. Experts from other specialties, such as Medicine and Orthopaedics, will be co-opted as necessary in the discussion and assessment of applications.
HA has been given additional funding on drugs by the Government this year (2010-11), part of which will be allocated to the spending on ERT for six types of rare metabolic Diseases including Mucopolysaccharidoses I, II and VI, Pompe Disease, Fabry Disease, and Gaucher Disease.

Appendix 3

Rare Disease and Orphan Drug Act

Article 1
This Act is enacted for the prevention and treatment of rare Diseases; for the early diagnosis of these Diseases; for the intensive care of rare Disease patients; for assisting patients gaining access to specific pharmaceuticals for the treatment of these Diseases and to special nutrient foods essential to the maintenance of life; and for promoting and ensuring the supply, manufacturing, and research and development of such pharmaceuticals and foods.For matters not regulated in this Act, regulations of other relevant Acts will apply.

Article 2
The competent authorities stipulated in this Act shall be the Department of Health of the Executive Yuan at the central government level; the municipal governments at the municipality level; and the county and city governments at the county and city level.

Article 3
The rare Diseases specified in this Act refer to Diseases with prevalence lower than that formulated and publicly announced by the central competent authority, and recognized by the Committee specified in Article 4 of this Act; or Diseases designated and publicly announced by the central competent authority under special circumstances.

Orphan drugs specified in this Act refer to pharmaceuticals with major indications for the prevention, diagnosis and treatment of rare Diseases that have been duly submitted in accordance with this Act for application and have been publicly announced by the central competent authority.

Article 4
To review and evaluate matters related to rare Diseases, the central competent authority shall set up a Committee for the Review and Examination of Rare Diseases and Orphan Drugs (hereafter referred to as the Committee). The organization and meetings of the Committee shall be regulated by the central competent authority.

Members of the Committee shall consist of representatives of government organizations, scholars and specialists in medical affairs, and impartial citizens. At least two-thirds of the members of the Committee shall be scholars and specialists in medical affairs.

Article 5
Missions of the Committee are:

1. Identification and control of rare Diseases;
2. Review and approval of orphan drug application;
3. Testing, marketing & registration of orphan drugs;
4. Review and examination of funding, research and development of orphan drugs;
5. Review and examination of the diagnosis, treatment, or international cooperation plans for rare Diseases, and issues concerning assistance and counseling;
6. Review and examination of the use of non-orphan drugs for the treatment of some specific Diseases; and
7. Other relevant issues.

In the execution of the aforementioned missions, the Committee shall consult other relevant scholars, specialists and representatives of industry or patients of rare Diseases for their opinions.

Article 6
The central competent authority may entrust institutions with projects concerning the control and research of rare Diseases.

Article 7
Medical personnel, upon identifying patients of such rare Diseases specified in Article 3, or human remains died of such Diseases, shall report to the central competent authority.

Article 8
The central and the municipal competent authorities, upon receiving reports or on identification of persons with genetic anomalies of rare Diseases, may, if need be, dispatch specialists from genetic health counseling centers for interviewing. They shall tell patients the relevant effects of the Disease.

Article 9
Organizations, institutions, and personnel authorized by this Act for the execution of functions specified in Article 8 and Article 9 shall be attentive to their attitude and methods of execution. They shall respect the will and dignity of the patients. They shall also protect the privacy and normal social functioning of the patients.

Article 10

The central and the municipal competent authorities shall encourage medical care institutions and research institutions at all levels to conduct the prevention and control of rare Diseases; and provide them funding for manpower development, research, and facilities.

Funds required for the aforementioned subsidies shall come from budgets of the central and the municipal competent authorities. Donations from organizations and groups concerned will also be solicited.

Article 11
The central and the municipal competent authorities shall organize and hold educational activities for the prevention and control of rare Diseases. These activities will be conducted with the assistance of organizations, schools, civil groups, and mass media.

Article 12
The central and the municipal competent authorities may entrust medical care institutions with the testing and treatment of rare Diseases.

Article 13
The central competent authority may assist institutions, reviewed and approved by the Committee with the following certificates, in their international medical cooperation programs:

1. certificates, applications, and medical care plans prepared by the medical care institutions or research institutions specified in Article 10 or Article 12 of this Act;
2. certificates or letters of consent issued by other national hospitals or research institutions
3. letters of consent signed by patient;
4. other necessary documents.

Items for the laboratory testing of the aforementioned medical cooperation programs may be done directly by the medical care institutions or research institutions specified in Article 10 or Article 12 of this Act. The central competent authority shall appropriately subsidize their costs.

Article 14
Unless otherwise regulated by this Act, orphan drugs shall not be manufactured or imported without the registration, market approval, and permit licenses issued by the central competent authority.

Article 15
Pharmaceuticals meeting one of the following criteria may apply for registration and market approval as orphan drugs.

1. The major indications of the medicinal products are for the prevention, diagnosis, and treatment of rare Diseases.
2. Medicinal products that have been approved by other countries to have major indications for the prevention, diagnosis, and treatment of rare Diseases.

Documents required for registration and market approval, review procedures, and other relevant issues shall be regulated by the central competent authority.

Article 16
In the application for registration and market approval of orphan drugs, the central competent authority may, if necessary, require the conduct of domestic clinical trials. Applicants shall adequately explain in public contents of the clinical trials and their results.

Article 17
Permit licenses issued in accordance with the registration and market approval of this Act for orphan drugs are valid for ten years. During this period, the central competent authority will not accept applications for registration and market approval of pharmaceuticals of the same kind.

If the manufacturing or importation of the aforementioned orphan drugs need to be continued after the permit licenses expire in ten years, application for extension must be made in advance to the central competent authority. Each extension shall not exceed five years. During the extension period, medicinal products of the same kind may apply to the central competent authority for registration and market approval.

If orphan drugs which have been issued permit licenses through registration and market approval in accordance with this Act are publicly announced by the central competent authority to be no longer designated as orphan drugs, the extension of their permit licenses shall be processed in accordance with the regulations of the Pharmaceutical Affairs Acts.

If owners of licenses issued under Paragraph 1 decide to terminate the manufacturing or importation of orphan drugs within the valid period, they shall notify the central competent authority in writing six months prior to such termination.

Article 18
Under either one of the following conditions, the central competent authority may, irrespective of the regulations of Paragraph 1 of Article 17, accept applications for registration and market approval of other pharmaceuticals of the same kind and issue them permit licenses.

1. The new applicants have in their possession authorized consent from right-holders of the orphan drugs duly issued through registration and market approval.
2. New applications for orphan drugs of same indications and similar quality and their safety and efficacy have been proved to be superior to those of the orphan drugs already issued licenses.
3. Permit license owners for orphan drugs fail to meet demands on the orphan drugs.
4. Prices of the orphan drugs are considered unreasonable by the central competent authority.

Regulations of the preceding Article will apply to permit licenses issued by the central competent authority through registration and market approval under subparagraph 2 through subparagraph 4 of the preceding Paragraph.

Article 19
Government organizations, medical care institutions, patients of rare Diseases and their families, and relevant foundations, societies, and associations, may apply on ad hoc basis to the central competent authority for permission for orphan drugs not yet processed through registration and market approval, or meeting one of the conditions specified in subparagraph 3 and subparagraph 4 of Paragraph 1 of the preceding Article. These orphan drugs shall not be for profit making.
The central competent authority may, if necessary, entrust or designate relevant institutions or groups to process the aforementioned ad hoc applications.
Documents required for ad hoc applications specified in Paragraphs 1 and 2, their review procedures, and other relevant issues shall be regulated by the central competent authority.

Article 20
When orphan drugs are proved to be unsafe or hazardous to health, the central competent authority may order pharmaceutical firms or ad hoc applicants to recall the orphan drugs in due time. If necessary, permits issued to the orphan drugs may be revoked.

Article 21
The central competent authority shall compile annual report of orphan drugs approved by this Act for marketing or on ad hoc basis. The report shall contain information on the amount taken, number of patients, any adverse reactions, and other relevant matters.
Pharmaceutical firms and ad hoc applicants shall submit relevant information for the aforementioned report.

Article 22
Regulations concerning registration and market approval and ad hoc application of this this Act shall apply to pharmaceuticals that are difficult to manufacture or import by regulations of the Pharmaceutical Affairs Act, but are reviewed and confirmed by the Committee to be beneficial to the medical care of certain specific Diseases.

Article 23
The central competent authority shall announce periodically the recognition, permission, revoking, and annulment of rare Diseases and orphan drugs.

Article 24
Fees for review, registration, or licenses shall be paid for applying for registration and market approval, conducting clinical trials, issuance and extension of permit licenses, and ad hoc applications, The fee schedule shall be determined by the central competent authority.

Article 25
The central competent authority may promote the supply, manufacturing, and research and development of orphan drugs. Regulations governing the recipients of incentives, ways of promotion, and matters to be followed by the recipients shall be decided by the central competent authority.

Article 26
Manufacturing and importation of orphan drugs without permission, or the sales, supply, dispensing, transportation, deposit, trading of stolen goods, transfer, or display for sale of orphan drugs known for not being permitted shall be punished according to the regulations of Article 82 and Article 83 of the Pharmaceutical Affairs Act.

Article 27
Any violations of the regulations of Article 16 shall be fined NT$ 30,000 to NT$ 150,000. For serious violations, pharmaceutical firms shall be suspended from making application for registration and market approval for the said pharmaceutical for two years. Medical care institutions may be suspended for one month to one year.

Article 28
In the case of submitting false documents for the application for registration and market approval of orphan drugs or extension of licenses for such orphan drugs, the applicants shall be fined NT$ 20,000 to NT$ 100,000, and shall be suspended from making application for registration and market approval of the said pharmaceutical for two years. Permit licenses already in the possession of the applicants shall be revoked. For their criminal responsibilities, they shall be sent to judicial organizations for further investigation.

Article 29

Any violations of the regulations of Paragraph 1 of Article 19 to allow orphan drugs approved on ad hoc basis for profit-making, the applicants shall be fined NT$ 30,000 to NT$ 150,000; the profits thus made shall be confiscated; and the applicants shall be suspended from making any ad hoc application for orphan drugs for two years.

Article 30

If orphan drugs ordered to be recalled in due time by the central competent authority under regulations specified in Article 20 are not recalled, the pharmaceutical firms or ad hoc applicants shall be fined NT$ 30,000 to NT$ 150,000, consecutively until the orphan drugs are recalled.

Article 31

Pharmaceutical firms in violation of the regulations of Paragraph 2 of Article 21 shall be fined NT$ 10,000 to NT$ 50,000. Ad hoc applicants in violation of such regulations, their future applications for orphan drugs shall not be permitted by the central competent authority.

Article 32

Fines regulated in this Act shall be administered by the central and the municipal competent authorities.

The aforementioned fines should be paid in due time. If not, the cases shall be transferred to the judicial court for enforcement by law.

Article 33

The central competent authority shall allocate budget to subsidize costs for the diagnosis, treatment, pharmaceuticals, and special nutrient foods essential to the maintenance of life not reimbursable according to the regulations of the National Health Insurance Act. Ways of subsidies, their contents, and other relevant issues shall be determined by the central competent authority.

Funds for the aforementioned subsidies may also be solicited from relevant organizations and groups.

Article 34

Special nutrient foods essential to the maintenance of life of patients of rare Diseases may be managed with reference to relevant regulations of this Act.

Article 35

The Enfercement Rules of this Act shall be formulated by the central competent authority.

Article 36

This Act shall become effective as of six months after the promulgation.

Article 37

The Executive Yuan shall review and amend this Act within six months after this Act is implemented for one year.

Appendix 4

Extracts from "Guidelines for treatment of Infantile-onset Pompe Disease through the Life Saving Drugs Program" Australia

Australian Government

Department of Health and Ageing

Guidelines for the treatment of Infantile-onset Pompe Disease through the Life Saving Drugs Program

This document outlines the criteria for initial and ongoing eligibility to receive Australian Government subsidised treatment with Myozyme® (alglucosidase alpha) through the Life Saving Drugs Program.

Currently, funds are specifically made available on an annual basis for the following therapies:

- imiglucerase (Cerezyme®) and miglustat (Zavesca®) for the treatment of Gaucher disease
- agalsidase alpha and beta (Replagal® and Fabrazyme®)for the treatment of Fabry disease
- laronidase (Aldurazyme®) for the treatment of Mucopolysaccharidosis Type I
- idursulfase (Elaprase®) for the treatment of Mucopolysaccharidosis Type II
- galsulfase (Naglazyme®) for the treatment of Mucopolysaccharidosis Type VI
- alglucosidase alpha (Myozyme®) for the treatment of Infantile-onset Pompe disease

Appendix A: Criteria for listing a drug on the Life Saving Drugs Program

1. There is a rare but clinically definable disease for which the drug is regarded as a proven therapeutic modality, ie. approved for that indication by the Therapeutics Goods Administration.

2. In epidemiological studies, the disease has been associated with a significant shortening of expected age-matched lifespan for those suffering from the disease and there is evidence to expect that a patient's lifespan will be extended as a direct consequence of the use of the drug.

3. A patient with the disease can be identified with reasonable diagnostic precision.

11. Estimated PBS Usage and Financial Implications

Based on the most conservative (highest) estimate of birth prevalence in the published literature, which is 1:100,000 (Martiniuk et al, 1998), the likely number of patients per year for infantile-onset Pompe disease was estimated to be up to 10.6 patients in Year 5. The submission's estimates did not include the currently known 20 late-onset patients in Australia.

The financial cost per year to the PBS was estimated to be less than $10 million in Year 5 for infantile-onset Pompe disease. For Late-onset Pompe patients, the average cost of treatment per year, based on 20 known Australian Pompe patients, was estimated to be an additional cost of between $10 - $30 million per year.

12. Recommendation and Reasons

The submission nominated standard (palliative) care as the comparator, which the PBAC considered was appropriate. Clinical evidence presented included two open-label observational studies (study 1602 and 2403) where treatment with alglucosidase alfa in infantile-onset Pompe disease was compared to a historical control group. The trials investigated survival, invasive ventilator-free survival and ventilator free survival. The results of these studies suggest that alglucosidase alfa prolongs survival in infants, but does not appear to extend the lifespan beyond early childhood. In addition, some patients experienced disease progression whilst on alglucosidase alfa, indicating that in those patients treatment with alglucosidase alfa delays the need for supportive care, rather than reducing the need for supportive care, as claimed in the submission. The Committee was unable to form a view on the clinical efficacy of alglucosidase alfa in late onset Pompe disease as there was insufficient data available at the time of submission. Any future data for late-onset Pompe disease would require evaluation in the form of a major submission.

A trial-based economic analysis was presented in the submission. The Committee noted that the economic evaluation included patients less than 26 weeks of age and no economic data were presented for late-onset Pompe disease. The analysis used a time horizon of 52 weeks (date of birth to 52 weeks), however the model used 52 weeks of treatment from the first infusion. However, the major limitation with the model is the short time horizon which does not capture the costs of ongoing treatment with alglucosidase alfa. As patients are not cured by treatment with alglucosidase alfa, ongoing treatment beyond 52 weeks is likely to be needed, resulting in escalating treatment costs. In addition, drug costs per year of treatment are also likely to escalate as the child grows. As alglucosidase alfa dosing is based on weight, the quantity of alglucosidase alfa required to treat an adult would be much higher than for an infant, resulting in a much higher treatment cost for late-onset Pompe disease.

The incremental cost per additional patient alive at 52 weeks is between $45,000 and $75,000 based on alglucosidase alfa treatment costs with supportive care cost offset (base case). This increases to between $75,000 – $105,000 for alglucosidase alfa treatment costs without the supportive care cost offset.