REPORT

Health **Technology** Assessment

ENZYME REPLACEMENT THERAPY FOR METABOLIC DISORDERS

HEALTH TECHNOLOGY ASSESSMENT UNIT
MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH

Authors:
Noormah Mohd Darus
Principal Assistant Director
Health Technology Assessment Unit
Medical Development Division
Ministry of Health

Sin Lian Thye
Nursing Sister
Health Technology Assessment Unit
Medical Development Division
Ministry of Health

EXPERT COMMITTEE
Dr Hussain Iman Hj Muhammad Ismail
Head of Department,
Senior Consultant Pediatrician and Pediatric Neurologist
Pediatric Institute
Kuala Lumpur Hospital

Dr Ngu Lock Hock
Consultant Pediatrician and Clinical Geneticist
Pediatric Institute
Kuala Lumpur Hospital

REVIEWERS
Prof Dr Thong Meow Keong
Senior Consultant Pediatrician and Clinical Geneticist
Department of Pediatric
University Malaya Medical Centre

Prof Dr Ong Lay Choo
Senior Consultant Pediatrician and Pediatric Neurologist
Department of Pediatric
Hospital Universiti Kebangsaan Malaysia

Datin Dr Rugayah Bakri
Head, Health Technology Assessment Unit
Deputy Director
Medical Development Division
Ministry of Health

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EXECUTIVE SUMMARY

The lysosomal storage diseases (LSDs) are a large group of disorders (>40 diseases) that is clinically heterogeneous but shares a common feature: they are all caused by the deficiency of a lysosomal enzyme or transport protein. This results in progressive intracellular accumulation of complex molecules that leads to tissue damage and, ultimately, organ failure. LSDs are rare and are considered as orphan diseases. As a group, LSDs occur in approximately 1 in 5000 to 8000 births. LSDs are severe, chronic, often progressive and life threatening. The onset of disease occurs frequently in childhood but late manifestation in adulthood is not uncommon. The quality of life of these patients and their families is often compromised due to the suffering of the disease and aggravated by psychosocial burden.

Gaucher disease is the most common glycosphingolipid storage disorder. This autosomal recessively inherited disease has high frequency (1/1,000 live births) in the Ashkenazi Jewish population, but is panethnic (1/50,000 live births). The disease results from defects in acid α-glucosidase(GCase) due to 200 different mutations at the "glucosidase, beta; acid (includes glucosylceramidase)" (GBA) locus. The lack of sufficient enzymatic activity leads to accumulation of glucosylceramide in the lysosomes of the macrophages and resultant visceral disease

Fabry disease is an X-linked, single-gene defect caused by a deficiency of lysosomal α-galactosidase A resulting in failure to catabolize α-D-galactosyl glycolipid moieties, mostly globotriaosylceramide. It is a panethnic disorder with an estimated incidence of 1 in 117 000 live births in males, but recent neonatal screening suggested an incidence of up to 1 in 3100 live births . Female heterozygotes often express delayed heterogeneous signs and symptoms ranging from no disease expression to fullblown disease as seen in hemizygous men

Pompe disease is a rare, progressive, and often fatal disease that can be diagnosed in infants, children, and adults. The underlying pathology is a deficiency or dysfunction of acid alpha-glucosidase (GAA), a lysosomal enzyme that hydrolyzes lysosomal glycogen to glucose. The combined incidence of all forms of Pompe disease varies, depending on ethnicity and geographic region, from 1:14,000 in African Americans to 1:100,000 in Caucasians. As with many rare genetic diseases, incidence data on Pompe disease are scattered and incomplete, with reported incidence ranging from one in 14,000 to one in 300,000, depending on the geographic area or ethnic group examined

Traditionally, most LSDs are incurable diseases without effective treatment. LSDs are often neglected and not a public health priority. However, scientific and medical advancement in the past two decades have brought hope to some patients. A few selected LSDs are now treatable with haematopoietic cell transplant (HCT) and enzyme replacement therapy (ERT). HCT requires matched-donor and is not an option for most patients. ERT involves regular intravenous administration of the deficient enzyme but is very expensive.

With respect to costs, figures from other countries show that for the teatment of Gaucher disease with enzyme repalcement therapy in Germany has annual costs averaging €75,000 to €300,000 or more per patient and in the United States, the annual cost of ERT ranges from US$40 000 – US$320 000. The mean cost per patient treated for fabry disease was

approximately £86,000 per annum in England and Wales. Current provision of ERT for fabry disease is said to cost the NHS in England and Wales around £20 million per annum.

For commissioners the challenge is how to fund treatment. At a cost of £30 000 - £100 000 ($50 000- 165 000; €42 000-140 000) per patient per year, these are among the most expensive licensed treatments available. If our society is committed to giving patients with rare diseases a fair deal, primary care trusts must make funds available for treatment. At present primary care trusts do not receive any "top sliced" central funding—yet the familial nature of lysosomal storage disorders means that a substantial financial burden can fall on an individual primary care trust. A wider use of consortia funding arrangements would allow individual primary care trusts to negotiate the budgetary hazards of having to fund enzyme replacement therapy.

In conclusion there was sufficient evidence to indicate effectiveness and safety of enzyme replacement therapy for Gaucher type 1 (non-neuronopathic), Fabry and Pompe (Infantile) disease. ERT has not been shown to be effective for other types of Gaucher and Pompe diseases.

The following is recommended:
- In Malaysia, several possible options for developing treatment policies that provide explicit criteria on whether or not funding should be available for ultra-orphan drugs in MOH by emulating the funding mechanisms of some countries in Europe, UK and Canada.
- A National ERT Advisory Committee can be set up that will evaluate each applicant for ERT. The suggested members of this committee are composed of experts in metabolic disorders, consumers' group representatives and government treasury officials. Those deemed to benefit most should be prioritized to receive therapy. Such prioritization process for eligibility of ERT should be in the purview of the Advisory Committee.
- Malaysia can also explore other treatment options, such as stem cell transplantation (SCT) instead of ERT for certain rare disorders to reduce cost although there is the issue of concern to find compatible donors.
- The Ministry of Health Malaysia may propose to the government to set up biotechnological companies to manufacture this ERT as a generic drug.
- Some local experts (personal communication) for our country recommend formulation of an Orphan Drug Act. The Act will help in establishing guidelines and regulations in terms of evaluating new treatment for rare disorders. It will set up a separate mechanism to fund treatment for these conditions that will be available to all patients who require them under the care of doctors trained and experienced in metabolic conditions
- A registry may be set up for rare conditions, in line with other disease registries already in existence in the MOH. Local data on the prevalence, incidence and other epidemiological data of lysosomal storage disease especially Gaucher, Fabry and Pompe disease for this country is needed.
- Further research could help to clarify the many uncertainties that exist. However, although doing so will be of clinical interest, it is questionable whether, within the current pricing environment, such research would have any substantive impact on policy decisions. The possible exception to this would be investigating the most efficient alternative treatment strategies for using ERT in a paediatric population.

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1.   INTRODUCTION

1.1   Background

The Lysosomal storage diseases (LSDs) are a group of conditions in which certain substances or substrates build up in compartments of the body's cells called lysosomes. Lysosomes contain enzymes that allow cells to digest and recycle the body's substrates, macromolecules. Missing, or poorly functioning enzymes that are unable to perform their normal activities cause LSDs. Over time, excessive amounts of the substrates accumulate and cause damage to the involved systems and organs in the body.

During the past 15 years, there have been remarkable advances in therapeutic options for LSDs. Nowadays; specific enzyme replacement therapies (ERTs) are available for several of these diseases. Enzyme replacement therapy (ERT) is a medical treatment replacing an enzyme in patients in whom that particular enzyme is deficient or absent. Usually this is done by giving the patient an intravenous (IV) infusion containing the enzyme. Enzyme replacement therapy is currently available for some lysosomal diseases: Gaucher disease, Fabry disease, Glycogen storage disease type II (Pompe disease). Enzyme replacement therapy does not "treat" the underlying disease, only the symptoms.

1.1.1   Gaucher's disease

Gaucher's disease is an inherited disorder caused by deficient activity of the enzyme glucocerebrosidase, found mainly in lysosomes. This results in an accumulation of glucocerebroside in the lysosomes of macrophages, predominantly in the reticuloendothelial system. Consequences of this abnormal storage include visceral problems: hepatomegaly,[1] splenomegaly, [2] anaemia and thrombocytopenia causing fatigue, discomfort, infections, bleeding and bruising; bone problems: pain (acute or chronic) and bone crises[3], neurologic manifestations [4] and avascular necrosis; other problems such as lung disease, impaired growth and delayed puberty. Cardiac alterations are not principal manifestations in most subtypes of Gaucher disease, but progressive heart valve calcification has been described in type 3 variants identified in Arab, Spanish, and Japanese patients.[5]

The severity of symptoms and rate of progression vary considerably from patient to patient. It ranges from asymptomatic to severe with early death. The variability is partly related to genotype (over 200 different mutations have been identified). Although, at a population level, different genotypes tend to be associated with certain phenotypes, making it difficult to generalise findings from one country to another, the relationship between genotype and phenotype is not rigid, as background genetics and environment also play a role. Prediction of the clinical course of an individual patient based on genotype alone is uncertain. [6-9]

Gaucher's disease is classified into three subtypes by clinical features [5]
- Type I (Non-neuronopathic form) can present at any age and has predominantly visceral symptoms without neurological effects. It is by far the most common form.It is often referred to as the "adult" form, although age at onset ranges from toddlerhood to old age; the rate of disease progression varies. Patients in this group usually bruise easily and experience fatigue due to anemia and low blood platelets. They also have an

enlarged liver and spleen, skeletal disorders, and, in some instances, lung and kidney impairment. There are no signs of brain involvement. Symptoms can appear at any age.

- Type II (Acute neuronopathic form): Have two forms: i) the "infantile" form is characterized by liver and spleen enlargement apparent by 3 months of age; rapidly progressing, severe central nervous system involvement, extensive and progressive brain damage and usually results in death before the age of two. ii) In the "neonatal" form, death occurs shortly after birth. It causes severe progressive brain disease and death occurs in infancy.

- Type III (Chronic neuronopathic form) *also* called the "juvenile and adult (cerebral)" form, progresses more slowly, with mild central nervous system involvement and onset usually occurring during early adolescence or young adulthood. Type 3 has three known variants: i) 3a, characterized by ocular motor apraxia, one neurologic sign (myoclonic seizures), and mild organ involvement; ii) 3b (also known as the Norrbottnian type, after the Swedish province where many cases have been reported), characterized by ocular motor apraxia and moderate-to-severe organ involvement; and iii) 3c, characterized by ocular motor apraxia and progressive calcification of the heart valves.

Gaucher disease is the most common glycosphingolipid storage disorder. This autosomal recessively inherited disease has high frequency (1/1,000 live births) in the Ashkenazi Jewish population, but is also panethnic (1/50,000 live births). [10]

1.1.2 Fabry's disease (Anderson Fabry Disease or AFD)

Fabry's disease is a fat storage disorder caused by a deficiency of an enzyme, alpha-galactosidase A (also called ceramidetrihexosidase), involved in the breakdown of fats. Since fat doesn't break down properly, part of it (globotriaosylceramide, also called Gb3 or GL-3) accumulates in organs of the body and causes damage. The disease usually presents in childhood, is progressive and results in increasing disability and premature death. [11-13]

It is a panethnic disorder with an estimated incidence of 1 in 117 000 live births in males, but recent neonatal screening suggested an incidence of up to 1 in 3100 live births . Female heterozygotes often express delayed heterogeneous signs and symptoms ranging from no disease expression to fullblown disease as seen in hemizygous men. [14-16]

The initial manifestations of Fabry disease are usually angiokeratoma and recurrent episodes of neuropathic pain in the extremities occurring during childhood or adolescence. [17-20] Most affected patients also exhibit a decreased ability to sweat. [17] As the disease progresses, renal function deteriorates, usually beginning in the third or fourth decade of life, and male patients often progresses to end-stage renal failure. Left ventricular hypertrophy, conduction defects and valvular abnormalities are also commonly seen,[21-23] as are structural and functional abnormalities of the cerebral circulation. Transient ischemic attacks and large and, small vessel strokes have been reported in both males and females. All of these classic signs and symptoms of Fabry disease have been reported in heterozygous females, but their onset

occurs on average about 10 years later than in males. [21] Renal, cardiac and cerebrovascular disease contribute to premature mortality at a median age of about 50–55 years in men and 70 years in women. [22 -23]

1.1.3 Pompe's disease

Pompe disease is a rare, progressive, and often fatal disease that can be diagnosed in infants, children, and adults. The underlying pathology is a deficiency or dysfunction of acid alpha-glucosidase (GAA), a lysosomal enzyme that hydrolyzes lysosomal glycogen to glucose. [24-25] Without this enzyme, glycogen accumulates in the lysosomes and leads to severe muscle degradation. It predominantly affects the heart, skeletal and respiratory muscles of the patient. When symptoms appear within a few months of birth, babies frequently display a markedly enlarged heart and die within the first year of life. When symptoms appear during childhood, adolescence or adulthood, patients may experience steadily progressive debilitation and premature mortality due to respiratory failure. They often require mechanical ventilation to assist with breathing and wheelchairs to assist with mobility. [26-28]

The two general subtypes of glycogen storage disease type II (GSD II), also known as Pompe disease, are suspected in individuals with the following findings:

Infantile-onset Pompe disease is suspected in infants with the following: [34]

- Poor feeding/failure to thrive (44%-97% of cases)
- Motor delay/muscle weakness (20%-63% of cases)
- Respiratory concerns (infections/difficulty) (27%-78% of cases)
- Cardiac problems (shortened PR interval with a broad, wide QRS complex, cardiomegaly, left ventricular outflow obstruction, cardiomyopathy) (50%-92%). Note: The characteristic ECG changes indicate accelerated atrioventricular conduction and may be considered diagnostic of Pompe disease. [29-30]

Late-onset (i.e., childhood, juvenile, and adult-onset) Pompe disease is suspected in individuals with proximal muscular weakness and respiratory insufficiency without cardiac involvement.

The combined incidence of all forms of Pompe disease varies, depending on ethnicity and geographic region, from 1:14,000 in African Americans to 1:100,000 in Caucasians. [28] As with many rare genetic diseases, incidence data on Pompe disease are scattered and incomplete, with reported incidence ranging from one in 14,000 to one in 300,000, depending on the geographic area or ethnic group examined. [31] The infantile-onset form has an apparent higher incidence among African Americans and in southern China and Taiwan, [31] whereas the late-onset adult form has an apparent higher incidence in the Netherlands. [32] The combined incidence of all forms of Pompe disease is estimated to be 1:40,000. [30]

1.1.4 Lysosomal storage diseases (LSDs) in Malaysia

A few selected LSDs are now treatable with haematopoietic cell transplant (HCT) and enzyme replacement therapy (ERT). HCT requires matched-donor and is not an option for most patients. ERT involves regular intravenous administration of the deficient enzyme but is very expensive. Currently selected treatable LSDs are as in table 1 below [33].

Table 1: Clinical manifestation if LSDs with possible treatment

Disease	Main clinical manifestation	HCT	ERT
Pompe disease	Infantile type: Hypertrophic cardiomyopathy, skeletal myopathy, fatal in first year of life Juvenile/adult-onset type: respiratory muscle weakness	No	Yes
Gaucher disease Type 1 (non-neuropathic)	Hepatosplenomegaly, anemia, bleeding tendency, bone fracture	Yes	Yes
Fabry disease	Adolescent/adult onset - renal failure, acroparesthesias, stroke	No	Yes

(a). Diagnostic facilities - The confirmatory diagnosis of LSDs requires specific enzyme assay in the leukocyte or cultured fibroblast. Currently the confirmatory diagnostic tests are not available locally. The tests need to be outsourced at international centre including:

(i). National Referral Laboratory, Department of Genetics Medicine, Women's and Children's Hospital, Adelaide, Australia.

(ii). Biochemical Genetics Laboratory, Department of Medical Genetics, National Taiwan University Hospital, Taipei, Taiwan.

Most of the time, the tests are requested and arranged by Clinical Geneticists at Kuala Lumpur Hospital (HKL). A total number of 95 tests were requested to the above centres in Australia or Taiwan as show in the table 2 below:

Table 2: test versus cost per patient

Test	Cost per patient
Leukocyte's lysosomal enzyme(s) assay (Set of 14 for the neurolipidoses screen)	AUS $ 300
To establish skin fibroblast culture for lysosomal enzyme(s) testing	AUS $ 370

At present, in HKL, there were 2 patients with Pompe disease - infantile type; 3 patients with Pompe disease - Juvenile/adult onset; 1 patient with Gaucher disease; 1 patient with Fabry disease and 20 patients with other non-treatable LSDs.

A few patients are diagnosed in other major referral hospitals such as Hospital Pulau Pinang, Hospital University Kebangsaan Malaysia (HUKM) and University Malaya Medical Centre (UMMC).

(b). Patients' Treatment Status (for treatable LSDs)

The first patient (Gaucher disease, UMMC) was treated in 1997. In 2006, 2 patients with Pompe disease were treated under Genzyme's International Charitable Access Program (ICAP). In 2007 Ministry of Health (MOH) approved a "Dasar Baru" programme for clinical genetic and metabolic service in Paediatric Institute, HKL. Three patients were approved for ERT under this programme.

Table 3: Type of LSDs patients treated with ERT

Disease	Institution	Age (yr)	Treatment status
Gaucher (type I)	HKL	child	Treated – funded by MOH
Gaucher (type I)	UMMC	adolescent	Treated – ICAP
Pompe (infantile- onset)	HKL	child	treated- initially ICAP, funded by MOH since 2007
Pompe (infantile- onset)	HKL	child	treated- initially ICAP, funded by MOH since 2007
Pompe (juvenile)	SGH	adolescent	Not treated
Pompe (juvenile)	SGH	adolescent	Not treated
Pompe (adult)	HKL	adult	Treated – ICAP
Pompe (infantile)	UMMC	infant	Treated – funded by UMMC
Pompe (infantile)	HUKM	infant	Treated by private hospital -died
Fabry *	HKL	adult	Not treated
			TOTAL

SGH: Sarawak General Hospital, Gz: Sponsored by Genzyme under its International Charitable Access Program (ICAP), * Patient also has breast cancer (stage 1)

(c). Costs of ERT

Table 4: Cost of drug per-vial and recommended dosage

Drug	Price	Recommended Dosage
Cerezyme (for Gaucher)	RM3,288.48 per vial (200 units)	30-60 units/kg every 2 weekly
Myozyme (for Pompe)	RM2,460.53 per vial (50mg)	20mg/kg every 2 weekly
Fabrazyme (for Fabry)	RM15,747.37 per vial (35mg)	1mg/kg every 2 weekly

2. TECHNICAL PROPERTIES OF ENZYME REPLACEMENT THERAPY

The lysosomal storage disorders are a group of 40 or so rare disorders, due to inherited deficiency of individual enzymes. Organ damage arises from progressive accumulation of the substrates for the missing enzyme. The commonest lysosomal storage disorders, with an incidence of 1 in 60,000 – 120,000, [16, 34] are Gaucher's disease (glucocerebrosidase

deficiency), Anderson-Fabry disease (alpha- galactosidase A deficiency), and Pompe disease (alpha-glucosidase enzyme deficiency)

2.1 Ceredase® or alglucerase

Ceredase® (alglucerase injection) is a modified form of the enzyme, ß-glucocerebrosidase (ß-Dglucosyl-N-acylsphingosine glucohydrolase, EC 3.2.1.45) used in the treatment of type-I Gaucher's disease. Alglucerase is a monomeric glycoprotein of 497 amino acids with carbohydrates making up approximately 6% of the molecule (Mr = 59,300 as determined by SDS-PAGE). The unmodified enzyme (ß glucocerebrosidase) also contains 497 amino acids and contains approximately 12% carbohydrate (Mr = 67,000). The carbohydrates on the unmodified enzyme consist of N-linked carbohydrate chains of the complex and high mannose type. Glucocerebrosidase and alglucerase catalyze the hydrolysis of the glycolipid, glucocerebroside, within the lysosomes of the reticuloendothelial system. [35]

Ceredase® is purified from a large pool of human placental tissue collected from selected donors. Steps have been introduced into the manufacturing process to reduce further the risk of viral contamination. However, no procedure has been shown to be very effective in removing viral infectivity. Ceredase® (alglucerase injection) catalyzes the hydrolysis of the glycolipid, glucocerebroside, to glucose and ceramide as part of the normal degradation pathway for membrane lipids. Glucocerebroside is primarily derived from hematologic cell turnover. [36]

Following an intravenous infusion of different doses (between 0.6 and 234 units/kg) of Ceredase® (alglucerase injection) over a 4-hour period, steady-state enzymatic activity was achieved by 60 minutes. Individual steady-state enzymatic activity and area under the curve of the activity increased linearly with the infused dose (0.6 to 121units/kg). Following infusion termination, plasma enzymatic activity declined rapidly with elimination half-life ranging between 3.6 and 10.4 minutes. Plasma clearance of Ceredase®, calculated from its plasma enzymatic activity, was variable and ranged between 6.34 and 25.39 mL/min/kg, whereas the volume of distribution ranged from 49.4 to 282.1 mL/kg. Within the dosage range of 0.6 and 121 units/kg, elimination half-life, plasma clearance, and volume of distribution values appear to be independent of the infused dose.

Ceredase® (alglucerase injection) is administered by intravenous infusion over 1-2 hours. Dosage should be individualized for each patient. Initial dosage may be as little as 2.5 units/kg of body weight 3 times a week up to as much as 60 units/kg administered as frequently as once a week or as infrequently as every 4 weeks. Disease severity may dictate that drug be initiated with relatively high doses or relatively frequent administration

Ceredase® (alglucerase injection) had FDA approval in April 1991.

2.2 Cerezyme® or imiglucerae

Cerezyme® is produced by recombinant DNA technology using mammalian cell culture (Chinese hamster ovary) used in the treatment of type-I Gaucher's disease. Purified imiglucerase is a monomeric glycoprotein of 497 amino acids, containing 4 N-linked

glycosylation sites (Mr = 60,430). Imiglucerase differs from placental glucocerebrosidase by one amino acid at position 495 where histidine is substituted for arginine. The oligosaccharide chains at the glycosylation sites have been modified to terminate in mannose sugars. The modified carbohydrate structures on imiglucerase are somewhat different from those on placental glucocerebrosidase. These mannose-terminated oligosaccharide chains of imiglucerase are specifically recognized by endocytic carbohydrate receptors on macrophages, the cells that accumulate lipid in Gaucher disease. [37]

Cerezyme (imiglucerase for injection) catalyzes the hydrolysis of glucocerebroside to glucose and ceramide. In clinical trials, Cerezyme improved anemia and thrombocytopenia, reduced spleen and liver size, and decreased cachexia to a degree similar to that observed with Ceredase (alglucerase injection).

Cerezyme ® (imiglucerase for injection) is administered by intravenous infusion over 1-2 hours. Dosage should be individualized to each patient. Initial dosages range from 2.5 U/kg of body weight 3 times a week to 60 U/kg once every 2 weeks. Cerezyme had FDA approval in May 1994.

2.3   Fabrazyme® or algasidase beta

Fabrazyme is recombinant human á-galactosidase an enzyme with the same amino acid sequence as the native enzyme. Purified agalsidase beta is a homodimeric glycoprotein. It is produced by recombinant DNA technology in a Chinese Hamster Ovary mammalian cell expression. Fabrazyme is intended to provide an exogenous source of a-galactosidase A in Fabry disease subjects. Preclinical and clinical studies evaluating a limited number of cell types indicated that Fabrazyme would catalyze the hydrolysis of glycosphingolipids including GL-3.

Fabrazyme is intended for intravenous infusion. The recommended dosage of Fabrazyme is 1.0 mg/kg body weight infused every 2 weeks as an IV. Fabrazyme had FDA approval in April 2003 [38-41]

2.4   Replagal

Replagal is used to treat patients who have Fabry disease, a rare inherited disorder. REPLAGAL contains 3.5 mg agalsidase alfa ghu, in 3.5 mL. It is an alpha-galactosidase-A enzyme preparation produced from human cell cultures through Gene Activation(R) technology. Patients with Fabry disease do not have enough of an enzyme, alpha-galactosidase A. This enzyme normally breaks down a fatty substance called globotriaosylceramide (Gb3). If the enzyme is not present, Gb3 cannot be broken down and it builds up in the cells, such as kidney cells. People with Fabry disease may have a wide range of signs and symptoms, including severe conditions such as kidney failure, heart problems, and stroke. Because the number of patients with Fabry disease is low, the disease is considered 'rare', and Replagal was designated an 'orphan medicine' (a medicine used in rare diseases) on 8 August 2000 in Europe. [43]

It is used as an intravenous infusion of 0.2 mg/kg body weight over 40 minutes given once every 2 weeks The European Commission granted a marketing authorisation valid throughout

the European Union for Replagal on 3 August 2001. The marketing authorisation was renewed on 2 August 2006 [43].

2.5   Myozyme® or alglucosidase alpha

Myozyme (alglucosidase alfa) consists of the human enzyme acid alpha-glucosidase (GAA), encoded by the most predominant of nine observed haplotypes of this gene. Myozyme is produced by recombinant DNA technology in a Chinese hamster ovary cell line. Alglucosidase alfa degrades glycogen by catalyzing the hydrolysis of alpha 1, 4 and alpha 1, 6 glycosidic linkages of lysosomal glycogen. Alglucosidase alfa has a specific activity of 3 to 5 U/mg (one unit is defined as that amount of activity that results in the hydrolysis of 1 μmole of synthetic substrate per minute under the specified assay conditions). Myozyme provides an exogenous source of GAA. Binding to mannose-6-phosphate receptors on the cell surface has been shown to occur via carbohydrate groups on the GAA molecule, after which it is internalized and transported into lysosomes, where it undergoes proteolytic cleavage that results in increased enzymatic activity. It then exerts enzymatic activity in cleaving glycogen. [44-46]

Myozyme (alglucosidase alfa) is indicated for use in patients with Pompe disease (GAA deficiency). 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 recommended dosage regimen of myozyme is 20 mg/kg body weight administered every 2 weeks as an intravenous infusion. The total volume of infusion is determined by the patient's body weight and should be administered over approximately 4 hours.

On April 28, 2006 the Food and Drug Administration granted marketing approval for Myozyme® (alglucosidase alfa) in the U.S. Myozyme is indicated for use in patients with Pompe disease (GAA deficiency).

3.   POLICY QUESTION

Should Ministry of Health Malaysia fund treatment cost for patient with metabolic disease in government hospital.

4.   OBJECTIVE
To determine the effectiveness, safety, cost implications of enzyme replacement therapy in metabolic diseases in government hospitals.

5.   METHODOLOGY

In general, Medline, Pubmed, Ebsco, Cochrane Library and HTA databases were searched from 2001-2007 inclusive. The key words used for search included: Enzyme replacement therapy, Enzyme Replacement Therapy for Gaucher disease, Enzyme replacement therapy for Fabry disease, Enzyme Replacement Therapy for Pompe disease, Cost effectiveness of enzyme replacement therapy, Strategies for enzyme replacement therapy, Cost of enzyme

replacement therapy, Models for enzyme replacement therapy, Policy on enzyme replacement therapy, prevalence on Gaucher disease, prevalence on Fabry disease and prevalence on Pompe disease etc. These words were used singly or in combination. Reference papers and cross references were accessed where applicable. Findings of papers are presented as general conclusions in some of the relevant areas involved.

A systematic review of all relevant literature was done and the evidence graded according to the modified Oxford scale (Appendix 1)

6. RESULTS AND DISCUSSION

6.1 Evidence about effectiveness

6.1.1 Effectiveness of ERT for Gaucher

Enzyme replacement therapy (ERT) is a promising therapeutic intervention for lysosomal storage diseases. Post-translationally engineered human α-glucocerebrosidase (Ceredase®/Cerezyme®) is commercially available and is the standard ERT for Type I Gaucher disease. Cessation of therapy is sometimes necessary for personal or financial reasons. In an article by Karen A. Grinzaid MS et al, it was shown that while on ERT for the first 3 years, liver and spleen volumes decreased, platelets and haemoglobin increased, and Angiotensin-converting enzyme (ACE) decreased to normal. During 1 year off therapy, platelet levels fell, spleen size increased almost twofold, liver size increased, and ACE increased four-fold. Hemoglobin remained stable. When ERT was reinstituted at 15 U/kg/2 weeks, liver and spleen volumes decreased, platelets increased, and hemoglobin and ACE remained stable. Magnetic resonance imaging (MRI) T1-weighted images indicated an increase in marrow signal after 1and 2 years of therapy. Regression of disease status in patients with Type I Gaucher disease after cessation of ERT conformed to the genotype–phenotype relationships of disease onset. Careful monitoring and reinstitution of ERT enabled previously attained treatment status. [47] Level 5

In the Health Technology assessment report by Connock M, Burls A, Frew E et al, one relevant RCT showed a potentially beneficial effect in two haematological surrogates (haemoglobin and platelet levels) and, to a lesser extent, on hepatomegaly. The other studies consistently demonstrated improvements in haematological parameters and in hepatomegaly and splenomegaly. Most measures of disease involvement on average tended to return towards normal in the majority of patients after about 1 or more years of treatment. For organomegaly and haemoglobin the rates and extent of response appeared greater the more abnormal the pre-ERT condition. Platelet levels appeared to improve more slowly and to a lesser degree the more severe the initial thrombocytopenia. Liver size in most cases approached 1.2 times that expected for body weight. Spleen enlargement appeared to reduce to between five and ten times normal in most patients. The effect of ERT on skeletal involvement also appeared to be positive in terms of pain, bone crises and fracture rate, but the quantitative evidence for these benefits was extremely weak. There was some evidence that ERT may exacerbate the depletion in bone density; thus, caution is needed in interpretation of results and careful monitoring is required. [10] Level 1

Quality of life improvements with ERT have been reported. Nonetheless, studies based on the ShortForm 36 (SF-36) indicate that patients treated with ERT continue to have reduced health-related quality of life (HRQoL) compared with the general population. No study attached utility values to quality of life measures for ERT-treated patients.

The severity of Gaucher disease is very variable. It was estimated that some 60% of patients, homozygous for the common $c.1226 C \rightarrow G$ (N370S) mutation, never come to seek medical attention. Accordingly, many—possibly most—patients with Gaucher disease require no treatment. In adults, the disease is rarely progressive. In children, the situation is different, and progression is common. It is only with proper awareness of the natural history of the disease that one can make rational judegments regarding who needs treatment. [34] Level 5

ERT leads to improvement of subjective symptoms, prevents progressive manifestations of Gaucher disease and alleviates Gaucher disease-associated anemia, thrombocytopenia, organomegaly, bone pain and bone crises. Many systemic manifestations seem to respond quite well to infusional therapy, with two exceptions: first, neurologic manifestations do not usually improve during ERT and second, if the level of fibrosis/inflammation has led to irreversible destruction of tissue, there will be no response to ERT. Examples are bone infarctions, a completely fibrous spleen, established pulmonary hypertension or liver cirrhosis. If any of these conditions is present or a deterioration of the disease occurs, investigations for amyloidosis, as a secondary complication of Gaucher disease, must be made. Some of the documented failures in the past might have resulted from inadequate dosages. It must be emphasized that, in contrast to other systemic manifestations of the disease, the neurological signs of Gaucher disease, especially type II and type III, do not respond adequately to enzyme supplementation therapy. This reflects a lack of understanding of the molecular basis of neurological Gaucher disease. [48] Level 5

Many patients with Gaucher's disease type I (for example, those who have high residual enzyme activity) are asymptomatic during childhood and early adult life, and some may present—with anaemia, thrombocytopenia, hepatosplenomegaly or bone disease, the clinical hallmarks of this condition—only in late adult life, often in their sixth or seventh decade. Many may never show symptoms. The benefits of enzyme replacement are not established for patients with very late onset disease or without symptoms. [49] Level 5

Although there is no doubting the efficacy of Cerezyme in Gaucher disease, there are clearly some limitations. The limited effect of ERT in disorders other than type 1 Gaucher's disease, which is caused by the primary involvement of only one type of cell (macrophages) is the inability of the infused proteins to reach critical organs and cells. [50]] Level 5 Not all patients are suitable for treatment, some organs and tissues are corrected more readily than others, and there are problems with gauging efficacy in these highly variable disorders. [51]] Level 5 The therapy is ineffective in neuronopathic Gaucher disease even if instilled directly into the cerebrospinal fluid (CSF) and has relatively poor efficacy against pre-existing bone and lung disease. Finally, the treatment is expensive and therefore, unless funded by charitable means, is unavailable to patients in countries that have more pressing health care concerns. [51] Level 5

6.1.2 Effectiveness of ERT for Fabry

Generally, focusing on ERT as a potential therapeutic intervention for Fabry disease, however, does not mean to exclude the development of other approaches, such as bone marrow transplantation therapy, enzyme enhancement therapy and gene therapy. The main limitations of ERT include the inability of recombinant enzymes to cross the blood–brain barrier for the treatment of Lysosomal diseases (LSDs) with primary neurological involvement. Although the treatment appears very promising, the lack of correlation between genotype and plasma or leukocyte α-Gal enzyme activities cannot give a reliable prediction of treatment outcome. Therefore long-term studies are required to evaluate the effect of ERT on critical clinical endpoints such as time to end stage renal disease, cardiac insufficiency, stroke, quality of life, and survival rate. Still a number of problems need to be solved for a clear definition of the therapeutic efficacy of ERT in the long term treatment of LSDs. [52] level 5

Beth L. Thurberg 2004 reported that the histologic study done confirmed the rapid and persistent efficacy of Fabrazyme by removing glycosphingolipid from the lysosomes of affected dermal tissues, and then maintaining the beneficial effects over at least 3 years. This study also confirmed that not all cell types respond equally to ERT. In the skin, as in the kidney, [53] level 5 the vascular endothelium was highly responsive to Fabrazyme therapy. Other cell types such as vascular smooth muscle and perineurium responded in a more gradual manner, but with significant and substantial substrate removal over the period of the study.

FDA approval of Fabrazyme was based on a randomized, double blind, placebo-controlled, multinational, multicenter study of 58 Fabry subjects, ages 16 to 61 years, all naïve to enzyme replacement therapy. The primary efficacy endpoint of GL-3 inclusions in renal interstitial capillary endothelial cells, was assessed by light microscopy and was graded on an inclusion severity score ranging from 0 (normal or near normal) to 3 (severe inclusions). A GL-3 inclusion score of zero was achieved in 20 of 29 (69%) subjects treated with Fabrazyme compared to zero of 29 treated with placebo. [54] Level 1c

All 58 subjects in the randomized study participated in an open-label extension study of Fabrazyme at 1.0 mg/kg every two weeks indefinitely. At the end of six months of open-label treatment, most patients achieved a GL-3 inclusion score of 0 in capillary endothelium. GL-3 was decreased to normal or near normal levels in mesangial cells, glomerular capillary endothelium, interstitial cells and non-capillary endothelium. GL-3 deposition was still present in vascular smooth muscle cells, tubular epithelium and podocytes, at variably reduced levels. Plasma GL-3 levels were reduced to levels below the limit of detection and remained so up to 18 months of treatment. [55-58] level 5, level 3b, level 1c

All subjects were pretreated with acetaminophen and an antihistamine to decrease or prevent infusion-associated reactions. Oral steroids were an additional option to the pretreatment regimen for patients who exhibited severe or recurrent infusion reactions.

In a systematic review, the Health Technology Assessment report by M Connock,1 A Juarez-GarciaA et al, the effectiveness of ERT for treating patients with Fabry's disease has been studied in three randomised placebo-controlled trials (total *n* = 70 patients; duration: 5–6 months) and 11 uncontrolled before–after studies (total *n* = 493 patients duration up to 24

11

months). A total of 119 patients were treated with Fabrazyme and the remainder with Replagal or human agalsidase alfa; most patients were male. The results suggested beneficial effects of ERT on measures of pain, cardiovascular function and some end-points reflecting neurosensory function. Renal function appeared to be stabilised by ERT. [59] Level 1

In another study by Maryam Banikazemi et al, where 82 adults with mild to moderate kidney disorder, Fabry disease, were recruited in a randomized (2:1 treatment-to-placebo randomization), double-blind, placebo-controlled trial; recruited from 41 referral centers in 9 countries (multicentre). Thirteen (42%) of the 31 patients in the placebo group and 14 (27%) of the 51 patients in the agalsidase-beta group experienced clinical events. The primary end was the time to first clinical event (renal, cardiac, or cerebro-vascular event or death. A renal event is an event with a 33% increase in serum creatinine level from baseline (2 consecutive values) or end-stage kidney disease, requiring long-term dialysis or transplantation. A cardiac event was defined as myocardial infarction or new symptomatic arrhythmia requiring anti-arrhythmic medication, pacemaker, direct current cardio-version, or defibrillator implantation; unstable angina defined by national practice guidelines and accompanied by electrocardiographic changes resulting in hospitalization; or worsening congestive heart failure requiring hospitalization. A cerebro-vascular event was defined as a stroke or transient ischemic attack documented by a physician. [60-61] level 1b, level 2c

Several investigators participating in this study have also noted, among some patients, improvement in specific clinical manifestations, including fatigue, exercise tolerance, abdominal pain, diarrhea, ability to sweat, and lymphedema. In addition, most patients report decreased and/ or less-frequent Fabry pain, but these findings have varied among patients. [58] Level 1c

Like all medical treatments, enzyme replacement therapies have some limitations. In Fabry's disease, for example, Gb3 is depleted in the vascular endothelium but largely unaffected in the kidneys or in cardiac myocytes. In disorders such as Fabry's disease, the damage in critically involved organs, such as kidneys, may not be reversible, and therefore a principal hope is the prevention of such damage. Beneficial functional effects may be more difficult to show than reduction in organ volume. Therefore, a particularly difficult challenge has been to choose valid clinical outcome measures that need to be disease-and organ-specific and include both reversible and preventable organ impairments. [50] Level 4

6.1.3   Effectiveness of ERT for Pompe

A majority of infants in whom ERT was initiated before age six months and before need for ventilatory assistance demonstrated improved survival, ventilator-independent survival, and acquisition of motor skills, and reduced cardiac mass compared to untreated controls. ERT can be accompanied by treatable infusion reactions as well as anaphylaxis. [28] Level 5

Like all lysosomal storage disorders, Pompe disease is best managed with a multidisciplinary treatment team coordinated by a physician with experience treating this rare disorder. Team members should include a professional geneticist (who may be the treating physician) in addition to the specialists dictated by the disease manifestations, who may include a cardiologist, neurologist, pulmonologist, respiratory therapist, physical therapist, occupational

therapist, speech therapist, and metabolic dietitian Currently, treatment options for Pompe disease are limited to supportive or palliative care. However, treatments that address the underlying cause of the disease are in development, most notably enzyme replacement therapy, which is in clinical trials, and gene therapy, [62] level 4 which is still in preclinical stages. Bone marrow transplantation has not been found to be effective because of poor enzyme penetration in muscle tissue. However, newer methods involving mesenchymal stem cell transplantation could be more successful. [63] Level 1c Supportive therapy greatly improves the quality of life for patients with Pompe disease and can minimize complications of the disease; however, it does not alter the disease course.

Enzyme replacement therapy for Pompe disease is intended to address directly the underlying metabolic defect via intravenous infusions of recombinant human GAA to provide the missing enzyme. Three recent open-label clinical trials involving a total of 15 infants [64-66] level 1c with infantile-onset Pompe disease (hypertrophic cardiomyopathy, severe GAA deficiency) showed that enzyme replacement can decrease cardiomegaly, improve cardiac and skeletal muscle function, and prolong survival.

In an open-label pilot study by J. M. P. Van Den Houti, A. J. J. Reuser et al, four patients with infantile Pompe disease were given α-glucosidase. The late-included patients had the poorest motor condition at the start of treatment. They were able to lift their arms only briefly, while their legs lay flat on the surface in a frog-like position without any movement. During the 36 weeks of treatment, the patients gained strength in their arms. They learned to play with toys above their head and to transfer objects. Head balance improved slightly. The best effect was seen in the two patients who were included early. At 36 weeks of treatment, the younger of the two could lift her legs freely from the surface and had learned to touch her feet in play. She turned her upper body completely, but was not able to roll over. Patient 1, who had the best motor condition at start of treatment, has shown the most remarkable progress. At 9.5 months of age, he learned to sit independently without arm support and at 10 months, he started to crawl. At 11 months, he pulled to a standing position and cruised along furniture. At 12 months, he learned to crawl in a four-point position and to stand with support of one arm The left ventricular mass index (LVMI) and left ventricular posterior wall thickness decreased significantly after start of treatment with rhAGLU. [64] Level 1c The largest reduction was seen in patient 4. At 36 weeks of treatment, the LVMI had decreased to 30% of the baseline value. Both the atelectasis of the left lung and the signs of cardiacinstability had disappeared. The combined effects of rhAGLU were life saving for this patient. [64] Level 1c

In another parallel phase I/II trial, reported by Amalfitano A, Bengur AR, Morse RP et al, 3 infants given twice-weekly infusions of recombinant human GAA manufactured in a Chinese hamster ovary cell line, showed a decrease in heart size and cardiac function remained normal; and glycogen deposits in skeletal muscle decreased markedly in one patient. All infants in both studies survived past the critical age of 1 year. [65] Level 1c

In a clinical trial or compassionate program reported by Van der Ploeg A, 18 juvenile and adult patients with severe Pompe disease were given 10 mg / kg weekly or 20 mg/kg biweekly myozyme ERT infusions for 6 months. At baseline, all patients were wheelchair bound. 10 of 17 patients demonstrated improvements in respiratory function, including a 50% reduction in required ventilation for one patient. Motor function improved for 13 of 18 patients, and stabilized in the remaining 5 patients; no declines in muscle strength or tone were noted.

Almost all 15/16 patients reported improvements in their quality of life since commencing ERT. [67] Level 1c

Overall, these preliminary results in infants suggest that the earlier enzyme replacement therapy is begun, the better the response. Other factors that could also affect outcome include stage of disease, genotype or presence of modifying genes or both, extent of muscle damage at start of therapy, and the immunologic status of the patient.

Administration of rhGAA to patients with a later onset of symptoms of Pompe disease was well- tolerated and led to early signs of benefit on skeletal and respiratory muscle function in the first 6 months to 10 months of treatment. [67-70] level 1c   A major problem for the evaluation of effectiveness of enzyme replacement therapy in adult Pompe disease was the lack of objective measures of muscle strength and function, and lack of questionnaires to evaluate activity and participation in patients with muscle disease. [71] Level 1c

Almost all patients reported positive improvements in their quality of life since commencing ERT. [68] level 1c In a study in adult-onset type II glycogenesis (Pompe) the MMT score improved in pelvic muscles in 3/5 patients and in leg and thigh muscles in all patients. Muscle MRI showed increased muscle bulk. [71] Level 1c

It would be hoped that if treatment were to be instituted during the preclinical phase, the patient would remain asymptomatic. For treatment, commencing after the threshold has been exceeded i.e. when the patient exhibits clinical signs, it would again be hoped that this would result in a return to an asymptomatic state, but in reality for most LSDs there would be a residual disease burden as with time most disorders are associated with irreversible damage. The size of the residual disease burden is critical in assessing the success or failure of an individual therapy. To give an example, some patients with infantile Pompe disease will continue to exhibit marked skeletal muscle dysfunction despite dramatic improvement in cardiomyopathy following ERT. If the skeletal muscle disease is severe enough to require full-time ventilation because of respiratory muscle weakness, the residual disease burden is enormous and many would doubt the efficacy of the underlying therapy, especially as it has to be maintained regularly at great expense. The end result of a variable residual disease burden in a group of heterogeneous disorders is the production of multiple, different, new clinical phenotypes whose natural history is unknown.

6.2   Safety

6.2.1   Safety of ERT for Gaucher

Different approaches have been used to manage ERT, comparable to the medical management of Crohn's disease. One strategy could be called *topdown*, with the dose being relatively high at the beginning and then subsequently tapered down to reach a maintenance phase. The other strategy could be called *step-up*, with the dose being relatively low at the beginning, and then being increased, if necessary, during the course of the disease. Both approaches have been compared in a recent study. Although showing similar results for hematologic and visceral parameters, a higher dose was more effective in improving surrogate parameters such as chitotriosidase and bone marrow involvement. There are very few data on tapering, but there

is some evidence that sudden cessation of therapy is generally not advisable, since rebound, phenomena can occur. [48] Level 5

As reported in a systematic review, The HTA 2006 done by Connock M, Burls A, Frew E, most studies did not report adverse events or reported that no serious events occurred. Adverse events appeared not to have been monitored systematically in any of the included studies. Lack of a systematic approach, short follow-up and small patient numbers mean that adverse events, if they occurred, may not have been detected or reported. Immunological reactions to intravenously infused protein can be anticipated. Seroconversion with immunoglobulin G (IgG) antibodies occurred in approximately 13% of patients (median time to conversion 6 months), was transient, lasting for few months, and was followed by tolerance. [10] level 1

Experience in over 1000 patients treated with Ceredase® has revealed a small number of adverse events. Some of these events were related to the route of administration including discomfort, pruritus, burning and swelling or sterile abscess at the site of venipuncture. The remaining experiences consisted of slight fever, chills, abdominal discomfort, nausea or vomiting. None of these events was judged to require medical intervention. Symptoms suggestive of hypersensitivity have been noted in a limited number of patients. Onset of such symptoms has occurred during or shortly after infusions; these symptoms have included pruritus, flushing, urticaria/angioedema (a small number of patients have had upper airway involvement), chest discomfort, respiratory symptoms, nausea and abdominal cramping. Hypotension has been reported to occur during a few of these events. Pretreatment with antihistamines and reduced rate of infusion has allowed continued use of Ceredase® in most patients. Additional adverse symptoms, which have been reported, include fatigue, vasomotor irritability or hot flash, weakness, headache, light-headedness, dysosmia, oral ulcerations, backache and transient peripheral edema, and diarrhea. Menstrual abnormalities and false positive pregnancy tests have previously been reported, but due to the introduction of manufacturing steps designed to reduce the level of hCG in Ceredase®, the likelihood of these occurrences is reduced. [72] Level 5

Approximately 15% of patients treated and tested to date have developed IgG antibody to Cerezyme® (imiglucerase for injection) during the first year of therapy. Patients who developed IgG antibody largely did so within 6 months of treatment and rarely developed antibodies to Cerezyme® after 12 months of therapy. Approximately 46% of patients with detectable IgG antibodies experienced symptoms of hypersensitivity. Patients with antibody to Cerezyme® have a higher risk of hypersensitivity reaction. Conversely, not all patients with symptoms of hypersensitivity have detectable IgG antibody. It is suggested that patients be monitored periodically for IgG antibody formation during the first year of treatment. Treatment with Cerezyme® should be approached with caution in patients who have exhibited symptoms of hypersensitivity to the product. Anaphylactoid reaction has been reported in less than 1% of the patient population. Further treatment with imiglucerase should be conducted with caution. Most patients have successfully continued therapy after a reduction in rate of infusion and pretreatment with antihistamines and/or corticosteroids. [37] Level 5

6.2.2   Safety of ERT for Fabry

Infusion-related reactions were the most common reported adverse event in the studies, occurring in 12–59% of patients. These were stated to be prevented by pre-infusion medication and milder with subsequent infusions. [59] Level 1

In a study by Raphael Schiffmann 2006, the results of this long-term, open-label study demonstrate that agalsidase alpha administered at a dose of 0.2 mg/kg by intravenous infusion over 40 min on an every-other-week basis was safe and well tolerated for up to 4.5 years and were able to transition to administration of their infusions in the home setting. Eight patients developed persistent IgG antibodies to agalsidase alpha, but IgE antibodies were not detected in any patient. The development of IgG antibodies appeared not to affect any clinical end points. Estimated GFR remained stable in subgroups of patients with Stage I (GFR >90 ml/min) or Stage II (GFR 60–89 ml/min) chronic kidney disease at baseline. [14] Intravenous infusions of a-gal A are safe and have widespread therapeutic efficacy in Fabry disease. [54] Level 1c

No significant changes from base line in the echocardiograms, electrocardiograms, or other safety assessments in either group were observed after 20 week in the double-blind study or after six months of the open-label study reported by Christine et al. The infusions were generally well tolerated. Rigors and fever were the only treatment related adverse events that occurred significantly more frequently in the recombinant *a*-galactosidase A group than in the placebo group. [55] Level 5

6.2.3   Safety of ERT for Pompe

Enzyme Replacement Therapy for pompe disease can be accompanied by treatable infusion reactions as well as anaphylaxis. [15, 68] level 1c Administration of rhGAA to patients with a later onset of symptoms of Pompe disease was well- tolerated. [67-69] Four patients developed anti-rhGAA IgG antibodies between weeks 8 and 16 with no signs of an inhibitory antibody effect in a study done by van Der Ploeg et al. [67] level 1c

The most serious adverse reactions reported with myozyme were cardiorespiratory failure and anaphylactic reactions. Cardiorespiratory failure, possibly associated with fluid overload, was reported in one infantile-onset Pompe disease patient, and pre-existing cardiac hypertrophy likely contributed to the severity of the reaction. Anaphylactic reactions have been reported during myozyme infusion. The most common serious treatment-emergent adverse events (regardless of relationship) observed in clinical studies with myozyme were pneumonia, respiratory failure, respiratory distress, catheter-related infection, respiratory syncytial virus infection, gastroenteritis and fever. The most common treatment-emergent adverse events (regardless of relationship) were fever, diarrhea, rash, vomiting, cough, pneumonia, otitis media, upper respiratory tract infection, gastroenteritis and decreased oxygen saturation. The most common adverse reactions requiring intervention were infusion-related reactions. [73]

6.3　Cost effectiveness of ERT

For most patients, the cost of enzyme replacement therapy has been between US $100,000 and USD $300,000 per patient per year.　Other treatments, including gene therapy and polyethylene glycol modified glucocerebrosidase, are currently being investigated as potentially more efficient and less expensive therapeutic alternatives

Cost effectiveness plays an important part in current decisions about the funding of health technologies. Drugs for rare disease (orphan drugs) are often expensive to produce and, by definition, will benefit only small numbers of patients. Several countries have put measures in place to safeguard research and development of orphan drugs, but few get close to meeting the cost effectiveness criteria for funding by healthcare providers. [74] level 4

6.3.1　Cost effective of ERT for Gaucher

The management of severe Gaucher's disease was dramatically improved by the development of enzyme replacement therapy.　However, this treatment is very costly (currently about $21,000 per infusion for adults at the starting dose recommended by the manufacturer). In Canada various agencies provided financial support for therapy, including both federal and provincial governments, private insurance carriers and the commercial supplier of the enzyme. In Ontario provincial health care officials accepted the development, by a multidisciplinary panel of medical experts, of formal guidelines for determining eligibility, on the basis of objective medical criteria, for reimbursement for enzyme replacement treatment. [75] Level 4
Between 1994 and 2005, IgG antibodies to imiglucerase were detected in approximately 15% of treatment- naive patients, although these usually did not affect efficacy of the infused enzyme. Still today, in Germany one unit of the enzyme costs an equivalent of about €6, making Gaucher disease one of the very expensive treatable orphan diseases, with annual costs averaging €75,000 to €300,000 or more per patient. [39] In the United States and Canada, for Gaucher's disease, in which it has been the most effective, the annual cost of ERT ranges from US$40,000 –US$320 000. [76] Level 4

The development of effective but very expensive therapies presents special problems for health care policy-makers, who are committed to ensuring access to new therapies but who are also under pressure to control overall health care spending. This pressure has spawned widespread interest in the economic assessment of new therapies. In Canada, guidelines have been proposed for this type of economic analysis, with particular emphasis on new pharmaceuticals. The process involves assessing the quality of the evidence for effectiveness and quantifying the incremental cost–utility ratio, in dollars per quality adjusted life-year gained.　Cost-effectiveness studies of enzyme replacement therapy for Gaucher's disease have consistently shown that the treatment is effective and safe, and this type of therapy is associated with a significant improvement in quality of life. However, it is also extremely expensive.　Estimates of the cost of the enzyme alone range from US$70 000 to US$550 000 per year for a typical adult with Gaucher's disease, depending on the dosage.　Laupacis and associates have suggested that a cost per quality-adjusted life-year of US$100 000 is beyond the limit of acceptable cost-effectiveness, whereas the US Public Health Service Expert Panel on Cost-Effectiveness in Health and Medicine has recommended against any preset threshold.
[76] Level 4

In the Health Technology Assessment 2006 report by Connock M, Burls A, Frew E et al cost estimates per quality-adjusted life-year gained ranged from £360,000 for the more aggressive disease genotype to £476,000 for the milder type; the average was £391,000. The authors pointed out that these estimates must be considered in the light of many caveats. [10] A Markov decision model was constructed based on patients moving between states defined by the modified severity score index (SSI). Most of the parameters were derived from the published literature. ERT was assumed to restore patients to full health in the base case. The estimated incremental cost per QALY [incremental cost-effectiveness ratio (ICER)] in the base case ranged from £380,000 to £476,000 per QALY, depending on genotype. [10] Level 1

Univariate sensitivity analyses examined ERT not restoring full health, more severe disease progression in the untreated cohort, and only treating the most severely affected patients. These produced ICERs of approximately £1.4 million, £296,000 and £275,000 per QALY, respectively. The base-case unit cost of the drug is £2.975.The unit cost would have had to be reduced ten-fold, to £0.30, to obtain an ICER of £30,000 per QALY. At a unit cost of £1 the ICER would be £120,000 per QALY. [10] level 1

6.3.2 Cost effectiveness of ERT for Fabry

The mean cost per patient treated for Fabry disease was approximately £86,000 per annum in England and Wales. The cost per patient varied considerably by dose. Current provision of ERT for fabry disease is said to cost the National Health Service (NHS) in England and Wales around £20 million per annum. Although this currently represents a steady state, if ERT reduces disease-specific mortality, the figure will grow as the population being treated ages. Extending use to patients who are mildly symptomatic or asymptomatic individuals as a prophylactic measure would also increase the burden on the NHS. [59] Level 1

The high cost of lifelong therapy with agalsidase beta is a major concern. The yearly cost of agalsidase beta for a patient weighing 70 kg is about $240 000 [10] level 1 and the annual cost of the treatment of Fabry disease with agalsidase alfa is over $250 000 per patient per year, depending on the weight of the patient. [77] Level 5 This suggests that lifelong therapy cannot be cost-effective even if it completely prevents the medical complications of Fabry disease and extends life for 30 years or more. [14] Level 5

ERT is currently expensive and cost-effectiveness studies have yet to be performed. However, the costs of this effective treatment for Fabry disease should be weighed against those of palliative treatment (for example, renal dialysis and transplantation, pacemaker insertion), institutional care following stroke, support from social services and the loss of productivity. Research currently underway into other potential treatments, such as gene therapy, may reduce the cost of treatment and perhaps lead to a cure for AFD. [16] Level 5 Research currently underway into other potential treatments, such as gene therapy, may reduce the cost of treatment and perhaps lead to a cure for AFD

The key assumptions were that ERT returns patients to full health and a normal life expectancy. As far as possible, all assumptions favoured rather than detracted from the value of ERT. ERT was assumed to restore patients to full health in the base case. The estimated

incremental cost-effectiveness ratio (ICER) in the base case was £252,000 per QALY. [59] Level 1

Univariate sensitivity analysis around the key assumptions produced ICERs ranging from £602,000 to £241,000. The base case unit cost of ERT was taken as £65.1/mg based on the cost of Fabrazyme. The unit cost would have had to be reduced to £9 to obtain an ICER of £30,000 per QALY. [58] Level 1c

6.4 Limitations of enzyme replacement therapy: Current and future

Clinicians, and certainly commissioners of ERT, often expect to see improvements in the patient's condition; for some disorders, particularly those at an advanced stage when starting therapy, this may be an unrealistic goal. The limitations of ERT in treating LSDs can be considered under two general headings: i) Limitations due to the nature of the disorders or our understanding of the diseases. ii) Limitations of the treatment itself. [78] For most of the disorders, we lack severity scores and biomarkers to allow us to judge the stage of the disease in the individual and also the efficacy of the therapy in reducing the disease burden. Severity scores have been published for Gaucher disease and Fabry disease, [79-80] but it is uncertain how widespread their use is outside the groups that developed them. [78]

Unfortunately, none of the currently prescribed ERTs is able to treat all aspects of the disorders equally. Experience has shown that bone, cartilage, heart valves and brain remain especially resistant to correction by intravenous ERT, and alternative methods of delivery or targeting will be needed if these problems are to be overcome. None of the ERT trials cited here includes patients with extensive brain involvement, which is prominent in many metabolic storage disorders. The reason for this limitation is that no enzyme given intravenously crosses the blood–brain barrier. [50] With regard to the skeletal disease, it remains unclear how much of the failure of ERT is due to the timing of therapy or the initiation of secondary events within the bones and joints.

As for limited budget impact, Hughes et al consider cost, divorced from any consideration of the opportunity cost. They observe that a drug costing £50,000 per patient per year; would only cost £2.5 million a year if there were only 50 patients to be treated. However, the cost should not be considered without reference to the value of what is foregone; £2.5 million would pay for over 520 hip replacements. [81]

Different localities have different health needs, priorities and budgets, and thus different commissioning decisions are made. Arbitrary national interventions to address legitimate variation can damage the development of local health services and the efficient use of limited resources. Whether the decision is made at a local or national level, the application of consistent, sustainable principles does not lead to a special status for treatments for rare diseases. Arguing for national policies is irrelevant to making the case for special status for treatments for rare diseases. [74, 81] Finally, the therapies are expensive, limiting access to patients from those countries that are able to afford expensive health care. [78]

Moreover, in Malaysia, for LSDs the diagnostic facilities are unavailable. In this case diagnosis may be problematic.

6.5   Policies of other countries

For commissioners the challenge is how to fund treatment. At a cost of £30 000-100 000 ($50 000- 165 000; €42 000-140 000) per patient per year, these are among the most expensive licensed treatments available. If our society is committed to giving patients with rare diseases a fair deal, primary care trusts must make funds available for treatment. At present primary care trusts do not receive any "top sliced" central funding yet the familial nature of lysosomal storage disorders means that a substantial financial burden can fall on an individual primary care trust. A wider use of consortia funding arrangements would allow individual primary care trusts to negotiate the budgetary hazards of having to fund enzyme replacement therapy. [49]

The quality of life for patients with Gaucher disease has been greatly improved by the development of enzyme replacement therapy. Given the small target population, these treatments are enormously costly on a per-patient basis. This brings us face-to-face with a major ethical dilemma. We do not put a price on human life. Yet health-care resources are a zero-sum game. What is spent on one disease cannot be spent on another. Is it better to treat one child with Hurler- Scheie disease, also called mucopolysaccharidosis I or to provide good prenatal care to 100 women who might not otherwise obtain it, or for that matter, to feed 1,000 malnourished children? These are difficult decisions that will be forced on us as enzyme replacement and other high-technology therapies come of age. [34]

Policy-makers are reluctant to make decisions based on the rule of rescue because of the potential for serious inequity: such decisions tend to be driven by emotional appeals, rather than by objective need. The outcomes of these decisions are also inherently unpredictable, and there is considerable potential for loss of control of expenditures. [76]

The resulting decision on funding must reflect the amount and quality of the evidence so that the decision is made in knowledge of the uncertainty around the estimate of cost effectiveness. Thus, even when the central estimate of the cost effectiveness is below the threshold for funding, if there is a large amount of uncertainty, the decision maker may still choose not to fund and await more evidence to reduce the uncertainty. [74]   Once a purely provincial initiative, the process is now sponsored by the federal government as the Common Drug Review (CDR). The CDR makes its recommendations for reimbursement based on a rigorous evaluation of cost-effectiveness that involves a review of the available clinical evidence and pharmacoeconomic data. This review is undertaken by the Canadian Expert Drug Advisory Committee with input from experienced external and internal reviewers. These difficulties of evaluation are due in part to the nature of rare diseases. The frequency of many of the disorders is so low that it is next to impossible in the short term to gather enough patients to achieve sufficient statistical power to demonstrate significant clinical benefits of a therapy. Moreover, the diseases are often complex and multisystem, and they tend to pursue highly variable clinical courses. The frequency of many of the disorders is so low that it is next to impossible in the short term to gather enough patients to achieve sufficient statistical power to demonstrate significant clinical benefits of a therapy. Moreover, the diseases are often complex and multisystem, and they tend to pursue highly variable clinical courses. [77]

Although ERT for treating the 'average' Gaucher's disease patient exceeds the normal upper threshold for cost-effectiveness seen in National Health Service (NHS) policy decisions by over ten-fold, some argue that since orphan drug legislation encouraged the manufacture of Cerezyme, and Gaucher's disease can be defined as an orphan disease, the NHS has little option but to provide it, despite its great expense

In a system with finite resources that do not meet all needs, money spent on one service means that some other service cannot be provided (opportunity cost) Commissioning decisions should not be posed as isolated questions but need to take into account other priorities A national decision to fund expensive enzyme replacement therapies for lysosomal storage disorders prevented primary care trusts funding other equally vital services. [82]

6.5.1   United Kingdom

In 2001, the West Midlands, United Kingdom was funding enzyme replacement therapy for Gaucher's disease, the only lysosomal storage disease that had a specific treatment at the time. In 2002, a new enzyme was licensed for Fabry's disease, and primary care trusts needed to decide whether to fund it. No comprehensive framework for making such decisions was in place. The potential effect of increasing numbers of high cost treatments is enormous. At the time, it was known that an enzyme replacement therapy for mucopolysaccharidosis 1 would shortly become available, and similar treatments for other lysosomal storage diseases were on the horizon. West Midlands primary care trusts decided, therefore, to develop a coherent commissioning approach to these orphan drugs that was compatible with their primary aim of providing comprehensive health care and their legal duty to stay within budget. After lengthy deliberations, it was concluded that rarity and being identifiable were not in themselves overriding factors to be considered in the decision of whether or not to fund treatment for a condition. No principled argument could be identified that distinguished patients with rare disease from those with common conditions, and all patients are potentially identifiable if they have a treatment need that is not being met. The cost effectiveness for all enzyme replacement therapies was over £200 000 ($350 000, €290 000) for each quality adjusted life year (QALY), well above the oft cited £30-40 000 UK threshold. The commissioning group's recommendation, endorsed by the boards of all 30 primary care trusts, was not to support funding of enzyme replacement therapy for Fabry's disease, mucopolysaccharidosis 1, and new patients with Gaucher's disease. The drugs were considered poorly cost effective. The potential long-term costs, possibly reaching £20m/patient, could not be justified on the grounds of equity given that many more patients, with equal capacity to benefit from treatment, would be deprived of treatments. [82]

There are now several different risk-sharing models in operation across the National Health System in UK. The simplest are based on a pooling of the total drug costs and the distribution of that cost across Primary Care Trusts (PCTs) in proportion to their share of the patient population. In October 2004, the Department of Health, UK wrote to the Chief Executives of all the PCTs and other relevant bodies to inform them that for a period of 2 years, from April 2005 to March 2007, six centres will be nationally designated and funded by the Department of Health, under the auspices of the National Specialised Commissioning Advisory Group, to provide a service for patients with lysosomal storage disorders. The service will include diagnostic, assessment and treatment services. This means that the cost of drug treatments,

including enzyme replacement therapies, will be funded on a national basis. What is important as a matter of principle with regard to access to treatment of other orphan diseases is that the announcement also made clear that "In the interim period between now and April 2005 when national funding commences, PCTs will be expected to respond in a timely fashion to consideration of requests from clinicians at the designated centres for funding for enzyme replacement therapies or equivalent treatments". [83]

6.5.2 Canada

Cost-effectiveness studies of enzyme replacement therapy for Gaucher's disease have consistently shown that the treatment is effective and safe, and this type of therapy is associated with a significant improvement in quality of life. However, it is also extremely expensive. Estimates of the cost of the enzyme alone range from US$70 000 to US$550 000 per year for a typical adult with Gaucher's disease, depending on the dosage. [34, 84] Laupacis and associates have suggested that a cost per quality-adjusted life-year of US$100 000 is beyond the limit of acceptable cost-effectiveness, whereas the Canadian Public Health Service Expert Panel on Cost-Effectiveness in Health and Medicine has recommended against any preset threshold. [85]

Because the cost per quality-adjusted life-year of enzyme replacement therapy for Gaucher's disease is above the level usually deemed cost-effective, in late 1992 the Ontario Minister of Health rejected appeals for public payment for the therapy. Policy-makers are reluctant to make
decisions on the basis of the rule of rescue because of the potential for serious inequity: such decisions tend to be driven by emotional appeals, rather than by objective need. The outcomes of these decisions are also inherently unpredictable, and there is considerable potential for loss of control of expenditures. The identification of clinical criteria for reimbursement, based on actual or anticipated severity of the disease, was therefore a critical element in the government's policy. Most patients with Gaucher's disease appear to be minimally symptomatic. The reimbursement program is intended to focus on those with severely disabling, if not life threatening, complications, such as severe anemia or thrombocytopenia, severe skeletal complications, or pulmonary hypertension. According to the policy, decisions regarding reimbursement are to be made on the basis of objective indicators of disease severity, as assessed by an advisory committee of medical experts. [76]

Some problems remain with the reimbursement policy. First, the objective indicators and clinical criteria used in the assessment of disease severity are based on our current understanding of the natural history of Gaucher's disease, which is widely acknowledged to be incomplete. More research is needed on this aspect of the disease and on the predictors of disease severity. Second, the medical advisors need reassurance that the overall assignment of resources for the reimbursement program is adequate to treat all patients who meet the criteria for disease severity. The system is working, for now, primarily because the amount set aside is adequate for reasonable reimbursement of all patients meeting the criteria, but problems could arise if the number of patients were to increase substantially. [76]

6.5.3 United States

Orphan drugs are reimbursed like all drug products in the USA. The government is not responsible for providing drugs to patients except in the case of parenteral medications to the Medicare (over 65 years of age) population. People must pay for their own drug prescriptions or their insurance may pay all or a proportion of the costs for the product. Consequently, access can be a problem. If an individual does not have sufficient funds to pay for their drugs, they may have to make some very difficult choices. However, virtually all the pharmaceutical companies have `give-away' programmes for truly needy individuals. These programmes are administered via a means test. The National Organization for Rare Disorders administers some of these needs programmes. [83]

6.5.4 Japan

In Japan, the cost of orphan drugs is usually covered by medical insurance, as for other drugs. Thus, the patient pays 20–30% of the cost and insurance companies pay the rest. However, in some cases, the amount to be paid by patients is limited by regulation to a certain amount, and the government pays the rest. In some other cases, the drug cost is fully covered by the government and medical insurance. [83]

6.5.5 Europe

6.5.5.1 Croatia

Because of high treatment cost, equal accessibility of enzyme-replacement therapy for all patients with Gaucher disease is endangered. In Croatia, they showed that, even in a financially burdened health care system, it is possible to finance such expensive treatments through establishing a separate fund. In this way, individuals with rare diseases are not left without medical benefits of state-of-the-art treatment just because the illness they suffer from is rare. According to the agreement between the Ministry of Health and the Croatian Institute for Health Insurance, each tertiary- level hospital in Croatia will be able to negotiate the cost of treatment for newly diagnosed patients with Gaucher disease. Hospital physicians have been informed of the existence of the fund. If they have patients with diseases requiring treatments that are on the list covered by the Fund, they need to submit a request to the hospital's Board for Pharmacotherapy at the beginning of the year. The Board forwards the requests to the Institute for Health Insurance, and can also suggest new drugs and new diagnoses. Any new requests outside this scheme have to be negotiated separately with the Institute or postponed until the beginning of the next year. [86]

6.5.5.2 France and Netherlands

In France, certain high-cost drugs are made available through specific centres, which receive extra funding to support their use. In the Netherlands, expensive licensed orphan drugs may be placed on a list that allows them to be prescribed by academic hospitals. 95% of the costs of the drugs on the list are reimbursed by the Ministry of Health, with the remaining 5% being paid from the hospital budget. The total costs of the orphan drugs are not allowed to exceed 5% of total hospital drug expenditure. [81]

There exist many obstacles in accessing marketed orphan products such as the time between obtaining the market approval and placing the product on the market, the reimbursement of these products, prescribing physicians' lack of experience concerning the medical benefits of these medicines and the absence of treatment consensus recommendations. According to Geoffrey, sustainable patient access is contingent upon the effective partnering of industry, patient groups and government along with the recognition of the three key components: central reimbursement, clinical expertise and monitoring. Using the Netherlands as a case example, he showed that models for a public-private partnership that support key elements of a sustainable system do exist. In the Netherlands, the orphan drugs steering committee works as the central reimbursement agency, the centre of excellence functions as the clinical expertise, and disease registries operate as the monitoring wing. [87]

For rare diseases it is not possible to compare outcomes with another treatment because often there is no other treatment available, and even animal models may not exist. The evidence base is sometimes very poor, and needs to grow while already helping patients in need. There is a great need for centres to collect patient data for research, documenting the incidence of disease and responses to treatment. Such centres would provide opportunities for clinical development and research, including patient registries and databases, and ways of collecting data in the post-approval setting.

In Europe, there is an additional problem that trials may need to be conducted across several member states in order to achieve adequate patient numbers. This can create difficulties in complying with local clinical trial regulations – a situation that creates delays and increases costs as patients may need to travel great distances on a regular basis, or even relocate for a year or more, in order to participate in an ongoing trial for a rare disease. Also, the newly adopted Clinical Trial Directive in the EU is currently in implementation in the member states legislation, and it is hoped that special provisions will be made for clinical trials involving rare disease, although at this time it is also possible that this would not be the case and that clinical trials for rare diseases could get even more complicated An important issue in Europe is that orphan drug legislation has been enacted at the EU level, but many of the laws and regulations associated with clinical trials, taxation, pricing and reimbursement are determined at member state level – and this can cause problems in interpretation or practical consequences of the orphan medicines regulation. [83]

7. CONCLUSION

In conclusion based on the above review focusing on Gaucher and Pompe diseases, it was found that there was sufficient evidence to indicate effectiveness and safety of enzyme replacement therapy for Gaucher type 1 (non-neuronopathic), Fabry and Pompe (Infantile) disease. However the effectiveness of the drug varies from person to person. Although clearly beneficial to such patients, enzyme replacement therapy treatment is very expensive.

7.1.1 Gaucher Disease:

Alglucerase (Ceredase) or imiglucerase (Cerezyme) are currently the only treatment available for Type 1 (non-neuronopathic) Gaucher disease. They have not been shown to reverse or

ameliorate neurological symptoms associated with Type 2 (acute neuronopathic) or Type 3 (subacute or chronic neuronopathic) Gaucher disease. Studies on children showed that ERT for Gaucher appears to normalise growth and possibly puberty. Delayed puberty was prevented when ERT was started in the first decade of life.

Organs in Gaucher diseased patients respond differently to ERT. Skeletal response to ERT is slower than haematological and visceral changes. Response of lung involvement to ERT is unpredictable. ERT is ineffective in treating neurological involvement due to the inability of the enzyme to penetrate the blood-brain barrier.

7.1.2 Fabry Disease

The marked pathological improvement in numerous vital organs after ERT leads us to believe that ERT should be able to drastically improve mortality and morbidity of Fabry disease related to coronary heart disease and cerebrovascular accident. Benefits in terms of improved quality of life, maintenance of renal function, improved electrocardiograph and echocardiograph results were demonstrated using fabrazyme (algasidase beta) or replagal. Certainly, ERT should be given early to patients with Fabry disease if resources allow before irreversible pathology sets in. When the disease progresses to the stage of chronic renal failure, it will obviously be too late as established renal pathology will be irreversible by whatever treatment

7.1.3 Pompe disease

Survival beyond one year with marked improvement of cardiac function was possible in Pompe diseased patients, which was a very important endpoint as historical cohort showed that death within the first year of life was almost invariable. 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. Myozyme provides great benefit especially when started early in the course of Pompe disease. The infant patients in those early trials showed major improvements in heart muscle function. A number of patients gained skeletal muscle function as well. Some of the infant patients who started on ERT began to walk independently. Of course, it is important to remember that once muscles are severely damaged, they cannot fully regain function.

7.2 Funding for treatment

The precise degree of health gain produced is uncertain because of the lack of adequate comparative studies and information about the natural history of the disease before the introduction of ERT. By increasing the number of patients being prescribed the treatment and, the likely increase in average dose per patient as young patients' progress to adulthood, will result in the potential long-term costs. Policy makers will have to consider whether the Ministry of Health Malaysia can afford such an expensive health care in the public hospitals in Malaysia

Several possible options are available for developing policies that provide explicit criteria on whether or not funding should be available for ultra-orphan drugs.

7.2.1 Alternative Funding Mechanism

- UK
  - Funding for ultra orphan drugs in the National Health System in UK are based on a pooling of the total drug costs and the distribution of that cost across Primary Care Trusts (PCTs) in proportion to their share of the patient population.
  - Risk-sharing schemes are a new approach to funding expensive medications with unproven effectiveness. Chapman described a risk-sharing scheme between a pharmaceutical company and an English Health Authority. [88] A guarantee on the performance targets was negotiated so that predictable health gains were achieved for a given drug expenditure.

- Canada
  - The present reimbursement program is adequate to treat all patients who meet the criteria for disease severity. The system is working, for now, primarily because the amount set aside is adequate for reasonable reimbursement of all patients meeting the criteria, but problems could arise if the number of patients were to increase substantially [76].

  - Eligibility for, and hence cost related to, ultraorphan drugs may be contained by specifying strict clinical criteria that extend beyond the licensing indications. In Ontario, Canada, for instance, reimbursement of enzyme replacement therapy for Gaucher's disease is based on actual or anticipated severity of the disease as assessed by an advisory committee of medical experts. [92] Most patients with Gaucher's disease are largely asymptomatic; only those with severely disabling, if not life-threatening complications, such as severe anaemia or thrombocytopaenia, severe skeletal complications, or pulmonary hypertension are eligible for province funded treatment. Pharmacogenetic tests that may allow potential responders to be identified are a complementary approach to clinical assessment.

- For the United States government
  - Orphan drugs are reimbursed like all drug products in the USA. The government is not responsible for providing drugs to patients except in the case of parenteral medications to the Medicare (over 65 years of age) population. People must pay for their own drug prescriptions or their insurance may pay all or a proportion of the costs for the product. If an individual does not have sufficient funds to pay for their drugs, they may have to make some very difficult choices. However, virtually all the pharmaceutical companies have `give-away' programmes for truly needy individuals. These programmes are administered via a means test. The National Organization for Rare Disorders, Inc. administers some of these needs programmes. [83]

- Japan
    - The cost of orphan drugs is usually covered by medical insurance. However, in some other cases, the drug cost is fully covered by the government and medical insurance.
- Some European countries:
    - In the context of equity and prioritization of health care, using a rights-based approach, in which individuals in a society are entitled to a decent minimum of health care, requires that treatment is made available for managing rare diseases. This is adopted in the EU legislation, which states that patients suffering from a rare condition should be entitled to the quality treatment as other patients.
    - Croatia:
        - The Ministry of Health and The Croatian Institute covered such expensive treatments through establishing a separate fund for Health Insurance.
    - France,
        - Certain high-cost drugs are made available through specific centers, which receive extra funding to support their use.
    - The Netherlands,
        - Expensive licensed orphan drugs may be placed on a list that allows them to be prescribed by academic hospitals. The Ministry of Health reimburses 95% of the costs of the drugs on the list, with the remaining 5% being paid from the hospital budget. The total costs of the orphan drugs are not allowed to exceed 5% of total hospital drug expenditure. [81]

7.3 Alternative treatment strategies

Elsewhere in other countries for example in UK and US, which explores other treatment options, stem cell transplantation (SCT) has been suggested to be an appropriate treatment option for a variety of genetic diseases, ranging from inherent defects of haemopoietic cell production or function to metabolic diseases mostly affecting solid organs.

Other options include a combination therapy, for example short course of ERT followed by stem cell transplantation.

7.4   Research

In UK, dedicated funding Clinical conditions, including cancer and diabetes, already have centralized funding to assist with service provision in meeting targets. The National Specialist Commissioning Advisory Group (NSCAG) supports specialist centres for ultra-orphan conditions at a limited number of English sites, and can provide Primary Care Organizations (PCOs) with contingency funding to support expensive treatments. Funding for some ultra-orphan drugs has recently been transferred from local budgets to central funding for a period of 2 years, relieving the pressure on those PCOs and Hospital Trusts with a cluster of patients due to hereditary characteristics. [95]

8. RECOMMENDATION

8.1 Treatment Policy

- In Malaysia, several possible options for developing treatment policies that provide explicit criteria on whether or not funding should be available for ultra-orphan drugs in MOH by emulating the funding mechanisms of some countries in Europe, UK and Canada.

- A National ERT Advisory Committee can be set up that will evaluate each applicant for ERT. The suggested members of this committee are composed of experts in metabolic disorders, consumers' group representatives and government treasury officials. Those deemed to benefit most should be prioritized to receive therapy. Such prioritization process for eligibility of ERT should be in the purview of the Advisory Committee.

- Malaysia can also explore other treatment options, such as stem cell transplantation (SCT) instead of ERT for certain rare disorders to reduce cost although there is the issue of concern to find compatible donors.

- The Ministry of Health Malaysia may propose to the government to set up biotechnological companies to manufacture this ERT as a generic drug.

- Formulation of an Orphan Drug Act is recommended by some local experts (personal communication) for our country. The Act will help in establishing guidelines and regulations in terms of evaluating new treatment for rare disorders. It will set up a separate mechanism to fund treatment for these conditions that will be available to all patients who require them under the care of doctors trained and experienced in metabolic conditions

8.2 Registry

A registry may be set up for rare conditions, in line with other disease registries already in existence in the MOH.

Local data on the prevalence, incidence and other epidemiological data of lysosomal storage disease especially Gaucher, Fabry and Pompe disease for this country is needed.

8.3 Research

In Malaysia, there is a need to establish a joint research body, involving the MOH and universities to research these conditions, using research funds either from MOSTI (Ministry of Science, Technology and Innovation) or from MOH.

Further research could help to clarify the many uncertainties that exist. However, although doing so will be of clinical interest, it is questionable whether, within the current pricing environment, such research would have any substantive impact on policy decisions. The

possible exception to this would be investigating the most efficient alternative treatment strategies for using ERT in a paediatric population.

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Appendix I- Levels of evidence scale
Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001)

Level	Therapy/Prevention, Aetiology/Harm	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval‡)	Individual inception cohort study with > 80% follow-up; CDR† validated in a single population	Validating** cohort study with good††† reference standards; or CDR† tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts††	All or none case-series	Absolute better-value or worse-value analyses ††††
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR† or validated on split-sample§§§ only	Exploratory** cohort study with good†††reference standards; CDR† after derivation, or validated only on split-sample§§§ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998.

Appendix 2 – Study protocol

HEALTH TECHNOLOGY ASSESSMENT PROTOCOL

ENZYME REPLACEMENT THERAPY IN METABOLIC DISEASES

1.   Introduction

The diseases that historically have made up Garrod's inborn errors of metabolism are due to defects in particular enzymes that result in the use of alternative metabolic pathways, the production of abnormal metabolites and frequently the aberrant storage of undigested materials. In many cases, it is the build up of these aberrant metabolites that are toxic to several organ systems. With extension of the lifespan of patients with these diseases through therapy, it has become increasingly evident that most metabolic diseases affect several organ systems. One such example is Galactosemia. When this life-threatening liver disease is prevented by dietary restrictions, additional manifestations develop in other organs such as the ovarian failure, which is unmasked by treatment. Although treatment of primary manifestations is an important approach with tremendous therapeutic value, to adequately address the multisystemic nature of these disorders it is important to develop methods to correct the basic defect systemically.

Ceredase, and then Cerezyme, to improve the symptoms of Gauchers disease, were the first two enzyme replacement therapies to be produced for treating an inherited lysosomal storage disorder. Because of the successful scientific and technological advances that led to their development and commercial success, similar treatments for other rare diseases are now being explored by scientists and the pharmaceutical industry.

1.1 Types of metabolic disorders

a. Gaucher's disease is an inherited metabolic disorder in which harmful quantities of a fatty substance called glucocerebroside accumulate in the spleen, liver, lungs, bone marrow, and sometimes in the brain. All Gaucher patients exhibit a deficiency of an enzyme called glucocerebrosidase that is involved in the breakdown and recycling of glucocerebroside. The buildup of this fatty material within cells prevents the cells and organs from functioning properly.There are three types of Gaucher disease. The first category, called **type 1**, is by far the most common. Patients in this group usually bruise easily and experience fatigue due to anemia and low blood platelets. They also have an enlarged liver and spleen, skeletal disorders, and, in some instances, lung and kidney impairment. There are no signs of brain involvement. Symptoms can appear at any age. In **type 2** Gaucher disease, liver and spleen enlargement are apparent by 3 months of age. Patients have extensive and progressive brain damage and usually die by 2 years of age. In the third category, called **type 3**, liver and spleen enlargement is variable, and signs of brain involvement such as seizures gradually become apparent.

b. Fabry's disease is a fat storage disorder caused by a deficiency of an enzyme, alpha-galactosidase A (also called ceramidetrihexosidase), involved in the breakdown of fats. Since

fat doesn't break down properly, part of it (globotriaosylceramide, also called Gb3 or GL-3) accumulates in organs of the body and causes damage. The disease usually presents in childhood, is progressive and results in increasing disability and premature death.

c. <u>Pompe's disease</u> is caused by deficiency in alpha-glucosidase enzyme. Without this enzyme, glycogen accumulates in the lysosomes and leads to severe muscle degradation. It predominantly affects the heart, skeletal and respiratory muscles of the patient. When symptoms appear within a few months of birth, babies frequently display a markedly enlarged heart and die within the first year of life. When symptoms appear during childhood, adolescence or adulthood, patients may experience steadily progressive debilitation and premature mortality due to respiratory failure. They often require mechanical ventilation to assist with breathing and wheelchairs to assist with mobility.

d. <u>Mucopolysaccharidosis I (MPS I)</u> is a progressive, debilitating and life-threatening disease. People with MPS I have an inherited disorder causing a deficiency of alpha-L-iduronidase, an important lysosomal enzyme. Hurler syndrome is the most severe of the MPS I forms. Affected children often die early from respiratory diseases and cardiac complications. Hurler-Scheie syndrome is less severe, but patients usually do not survive beyond their early 20's. Scheie syndrome is the mildest form with many patients living well into adulthood, but these patients can still have deformities, heart disease and difficulty breathing. According to the National Institutes of Health, studies in Canada estimate one in 100,000 babies born has Hurler syndrome. The estimate for Hurler-Scheie syndrome is one in 115,000 and for Scheie syndrome, it is one in 500,000.

e. <u>Maroteaux-Lamy syndrome</u> is a rare genetic metabolic disorder that belongs to a group of disorders known the mucopolysaccharidoses. The disorder is also known as mucopolysaccharidosis (MPS) type VI. Maroteaux-Lamy syndrome occurs in three types: a classic severe type, an intermediate type, and a mild type. The syndrome is characterized by a deficiency in the enzyme arylsulfatase B (also called N- acetylgalactosamine-4-sulfatase), which leads to an excess of dermatan sulfate in the urine. In general, growth retardation occurs from two to three years of age, with coarsening of facial features and abnormalities in the bones of hands and spine. Joint stiffness also occurs. The intellect is usually normal.

1.2 Types of synthetically prepared enzymes to replace absent/ defective enzyme production in metabolic/ lysosomal storage diseases

a. Ceredase® or alglucerase
-modified form of beta-glucocerebrosidase, used in the treatment of type-I Gaucher's disease.

-prepared from human donor tissue (human placenta isozyme protein)-??risk of viral contamination

-ceredase® catalyzes the hydrolysis of glycolipid, glucocerebrosidase to glucose and ceramide

-IV infusion over 1 to 2 hour period usually every 2 weeks. The frequency may be as often as EOD or only every 4 weeks based on the response or condition

-Had FDA approval in April 1991.

b. Cerezyme® or imiglucerae
-recombinant form of beta-glucocerebrosidase produced in Chinese hamster ovary cell line.
-used in the treatment of type-I Gaucher's disease.
-cerezyme catalyzes the hydrolysis of glucocerebrosidase to glucose and ceramide. Improved anemia and thrombocytopenia, reduced spleen and liver size and decreased cachexia to a degree similar to ceredase®.
-Had FDA approval in May 1994.

c. Fabrazyme® or algasidase beta
-recombinant human alpha-galactosidase A enzyme produced in Chinese hamster ovary cell line.
-used in the treatment of Fabry's disease.
-fabrazyme® reduces globotriaosylceramide (GL-3) deposition in capillary endothelium of the kidney and certain other cell types.
-IV infusion every 2 weeks (slow infusion)
-FDA approved April 2003

d. Myozyme® or alglucosidase alpha
-recombinant human enzyme acid alpha-glucosidase (GAA) produced in Chinese hamster ovary cell line.
-used in the treatment of Pompe's disease
-IV infusion over 4 hours every 2 weeks
-FDA approved 28 April 2006

e. Aldurazyme® or laronidase

-recombinant human alpha-L-iduronidase produced in Chinese hamster ovary cell line.
-used in the treatment of mucopolysaccharidosis I (MPS I) including Hurler's disease
-exogenous enzyme for uptake into lysosomes and increase the catabolism of glycosaminoglycans (GAG)
-IV infusion over 3-4 hours every week.
-FDA approved April 2003

Naglazyme™ or galsulfase

- used in the treatment of mucopolysaccharidosis IV (Maroteaux-Lamy syndrome)
- exogenous enzyme for uptake into lysosomes and increase the catabolism of glycosaminoglycans (GAG)
-IV infusion over 3-4 hours weekly
-FDA approved May 2005

2.   Policy Question

Should enzyme replacement therapy in metabolic diseases be practiced in government hospital? Is enzyme replacement therapy cost effective in government hospitals?

3.   Objective

To determine the effectiveness, safety, cost implications of enzyme replacement therapy in metabolic diseases in government hospitals.

4.   Scope

Hospital setting especially the pediatric department and home care.

5.   Considered aspects

1. Effectiveness.
2. Safety
3. cost implications
4. Social Perspective
5. Organizational implications.

6.   Strategy

To do new Health Technology Assessment

7.   Methodology

1. Retrieval of existing Health Technology Assessment if available
2. Retrieval of evidence
3. Analysis of evidence
4. Health Technology Assessment writing
5. Feedback on draft report and preparation for final report
6. Presentation on draft reports to Health Technology Assessment Council.
7. Presentation of reports to Technical Advisory Committee.
8. Approved policy sent to implementing agency.

Appendix 3- Evidence Table
Evidence table: Gaucher's Disease
Question: Is Enzyme Replacement   Therapy   in Gaucher disease safe, effective and cost effective.

Bibliographic/citation	Studytype	LE	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1)R. P. Hayes, K.A.Grinzaid et al HThe impact of gaucher disease and its treatment on Quality of life.Quality of Life Research 7,pp521-534	Descriptive	2c	16 participants from an ongoing study "dose Response to Enzyme Replacement Therapy in Gaucher Disease"	Type 1 gaucher Disease with symptoms: • Liver volume >1.5 times normal / Spleen Volume > 5 times normal / splenctomy • Evidence of Gaucher Disease by bone imaging • Anemia / thrombocytopenia	Enzyme replacement therapy			- Physical health limited their future plans/ career/sports activities/ physical activities - Apprehension related to receiving infusion in medical setting. - Drugs are expensive- anxiety related to financing treatment	Instrument used for HRQoL needs to be improved
2) By Elvira Ponce, Jay Moskovitz, and Gregory Grabowski Enzyme Therapy in Gaucher Disease Type 1: Effect of Neutralizing Antibodies to Acid b-Glucosidase. Blood, Vol 90, No 1 (July 1), 1997: pp 43-48	Case reports	4	2 patients	Case 1 is a 22-year-old Jewish man who was diagnosed withGaucher disease due to hepatosplenomegaly at 10 years of age diagnosis was confirmed by demonstration of decreased acid b-glucosidase activity in lymphocytes and the identification of homopretreatzygosity for the N370S allele. His younger brother, age 20, also hasGaucher disease type 1. Case 1 and his brother have Hashimoto's thyroiditis. At 18.5 yearsof age, case 1 began enzyme therapy (50 U/kgevery 2 weeks), because of massive splenomegaly (13 fold normal) and thrombocytopenia (21,000/mL). Case 2 is a 13-year-old Hispanic/German girl who was diagnosedat age 11 years with Gaucher disease due to asymptomatic splenomegaly. This diagnosis was confirmed by the deficient activity of acid b-glucosidase in lymphocytes and	enzyme therapy (50 U/kgevery 2 weeks), for case 1 enzyme therapy (30 U/kg every 2 weeks) for case 2	None	2 years for case 1 1 year for case 2	For case 1 • Anti–acid b-glucosidase antibody (IgG) was detected within the first 7 months. • He had experienced no improvement of his Gaucher disease over 26 months of enzyme therapy this treatment was discontinued For case 2 • During the first 6 months of enzyme therapy she showed substantial improvement particularly in her energy level, diminution in bone pain and partial regression of splenomegaly. • From 6 to 12 months ofenzyme therapy, the splenic volume decreased by 35% to 38%,respectively, from initial and the liver volume remained essentially • case 2 initially therapy showed a favorable response to enzyme therapy that plateaued after 1 year of	

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Bibliographic/citation	Studytype	LE	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
				the presence of one N370Sallele. She began progressive thrombocytopenia, increasing bone pain (particularly inthe knees), and the progressive hepatosplenomegaly enzyme therapy (30 U/kg every 2 weeks) due to severe fatigue				treatment An immunosuppression/ tolerization protocol was initiated in case 2 because of disease progression and stable neutralizing antibody titers The development of neutralizing antibodies in these two patients highlights the need for continuing close monitoring of patients during the initial phases of therapy since most patients become antibody positive during their first 6 to 9 months	
3) Jennifer J. MacKenzie, Dominick Amato, Joe T.R. Clarke,et al .Enzyme replacement therapy for Gaucher's disease: the early Canadian experience. CMAJ • NOV. 17, 1998; 159 (10)	Descriptive study	4	25 patients with Gaucher's disease in July 1995	Each questionnaire was identified by a number and the patient's initials. Besides the age, sex and ethnic background of the patient, the questionnaire collected information on the age at diagnosis, the genotype and whether the patient had undergone splenectomy. Information obtained with respect to enzyme therapy included the indication for therapy, the age at which therapy was begun, dosages of alglucerase, outcomes of therapy and any adverse reactions. The sources of financial support for therapy were also identified	Twentyfour were receiving the purified human product, alglucerase, and 1 was receiving the recombinant product, imiglucerase. The initial dosage varied from less than 19 to 80 units/kg every 2 weeks, the most common dosage being 24 to 30 units/kg every 2 weeks	none	The longest duration of therapy among the 25 patients was 56 months	*19 patients showed objective clinical improvement (i.e., elevation of hemoglobin concentration or platelet count, or both, decrease in organomegaly, decreasein number of bony crises and improvement of growth) Out of the 25 patients: • 2 patient's condition improved initially then deteriorated after the dosage of alglucerase was decreased. • The condition of another patient, who initially received a low dose thrice weekly, became worse with therapy. • 1 patient showed no change after 4 months of therapy. • Seventeen patients reported subjective improvement (4 apparently experienced no perceptible change). • For the remaining 4, no information was reported. Adverse reactions were rare, Reimbursement of the costs of therapy varied markedly from patient to patient and from place to place across the country (provincial government. Pharmaceutical manufacturer in addition to other supportprivate health insurance)	The condition of only 25 was considered severe enough to warrant such expensive treatment. Because the Health Protection Branch for general use by physicians had not yet approved the treatment, at the time, it was introduced into this country, systems of third-party payment, public or private, based on accepted formularies of approved medications did not apply. Moreover, because the delivery of this aspect of medical care is organized by province, how the matter might be handled in different parts of the country could vary considerably. There were marked variation in the dosages of enzyme and treatment schedules used in different centres,

Bibliographic/citation	Studytype	LE	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
									even between different patients treated at the same centre. this was driven by delays in or inadequate financial support for full-dosage treatment

Evidence table: Fabry's disease

Question: Is Enzyme Replacement Therapy in Fabry's disease effective, safe and cost effective?

Bibliographic/citation	Study type	LE	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size
1 Christine M. Eng et al, Safety and Efficacy of Recombinant Human α-Galactosidase A Replacement Therapy in Fabry"s Disease N Engl J Med, Vol. 345, No. 1 July 5, 2001	randomized, placebo-controlled, double-blind study of 58 patients who were treated every 2 weeks	1b	58, age 16-61 years. 56 male and 2 female	Eligible patients had an enzymatically confirmed diagnosis of classic Fabry's disease, had a level of activity of α-galactosidase A of less than 1.5 nmol per hour per milliliter in plasma or less than 4 nmol per hour per milligram in leukocytes, and were at least 16 years old. Patients were excluded if their serum creatinine concentration exceeded 2.2 mg per deciliter (194.5 μmol per liter), if they were undergoing dialysis, or if they had undergone kidney transplantation.	29 patients randomly assigned to receive recombinant α-galactosidase A (agalsidase beta; Fabrazyme, Genzyme, Cambrideg, Mass) at a dose of 1 mg per kilogram of body weight Intraveanously at rate of 0.25 mg per minute every other week for 20 weeks (total 11 infusion)	29 patients in the placebo group (phosphate-buffered mannitol).	20 weeks	• The primary efficacy end point was the percentage of patients in each group who were free of microvascular endothelial deposits of globotriaosylceramide in renal-biopsy specimens (i.e., who had a score of 0) after 20 weeks of treatment (11 infusions) in the double-blind study. • The end point was reached by 20 of the 29 patients in the recombinant α-galactosidase A group (69 percent), as compared with none of the 29 patients in the placebo group (P<0.001). • Safety: No significant changes from base line in the echocardiograms, electrocardiograms, or other safety assessments in either group were observed after 20 week *in* the double-blind study or after six months of the open-label study. The infusions were generally well tolerated. Rigors and fever were the only treatment trelated adverse events that occurred significantly more requently in the recombinant *a*-galactosidase A group than in the placebo group
2 Maryam Banikazemi et al. Agalsidase -Beta Therapy for Advanced Fabry Disease16 January 2007 Annals of Internal Medicine Volume 146 • Number 2	Randomized (2:1 treatment-to-placebo randomization), double blind, placebo-controlled trial. 41 referral centers in 9 countries.(multicentre)	1b	82 adults with mild to moderate kidney disorder, fabry disease, no previous ERT	At least 16 years, clinical evidence of Fabry disease Baseline characteristic similar except for proteinuria 82 adults with mild to moderate kidney disease. Six patients withdrew	Intravenous infusion of agalsidase beta (1 mg per kg of body weight) or placebo every 2 wweeks for up to 35 months (median, 18.5 months) 41 referral centers	31 patients in the placebo group	35 months	The primary end point was the time to first clinical event (renal, cardiac, or cerebrovascular event or death. - a renal event is an event with a 33% increase in serum creatinine level from baseline (2 consecutive values) or end-stage kidney disease requiring long-term dialysis or transplantation. - a cardiac event was defined as myocardial infarction; new symptomatic arrhythmia requiring antiarrhythmic medication, pacemaker, direct current cardioversion, or defibrillator implantation;

Bibliographic/citation	Study type	LE	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size
				before reaching an end point: 3 to receive commercial therapy and 3 due to positive or inconclusive serum IgE or skin test results. Three patients assigned to agalsidase beta elected to transition to open-label treatment before reaching an end point.	in 9 countries			unstable angina defined by national practice guidelines and accompanied by electrocardiographic changes resulting in hospitalization; or worsening congestive heart failure requiring hospitalization. - A cerebrovascular event was defined as a stroke or transient ischemic attack documented by a physician. Patients were allowed to transition to open-label agalsidase beta after an independent adjudication board confirmed that a primary end point event had occurred.. Thirteen (42%) of the 31 patients in the placebo group and 14 (27%) of the 51 patients in the agalsidase-beta group experienced clinical events. Primary intention-to-treat analyses shown agalsidase beta delayed the time to first clinical event (hazard ratio, 0.47[95% CI, 0.21 to 1.03'; P=0.06). Secondary analyses of protocol-adherent patients showed similar results (hazard ratio, 0.39 [C, 0.16 to 0.93]; P=0.034] Most treatment-related adverse events were mild or moderate infusion-associated reactions, reported by 55% agalsidase-beta patient and 23% placebo patient. Agalsidase-beta therapy slowed progression to the composite clinical outcome of renal, cardiac and cerebrovascular complications and death compared with placebo in patients with advanced Fabry disease. Therapeutic intervention before irreversible organ damage may provide greater clinical benefit.
4. Raphael Schiffmann, Markus Ries et al. Long-term therapy with agalsidase alfa for Fabry disease: safety and effects on renal function in a home infusion setting. Nephrol Dial Transplant (2006) 21: 345–354	This was a single centre, prospective open label treatment trial in 25 adult male Fabry patients who had completed a 6-month randomized placebo controlled study and subsequently enrolled in an open label extension study. Study patients were exclusively adult homozygous males and all had to have neuropathic pain at the start of the original study as a requirement for enrollment	1c	25 adult male Fabry patients	Twenty-two patients had infusions in the home setting. A total of 1528 home infusions were administered (range of 42–73 infusions per patient). No additional safety concerns were raised by administration of agalsidase alfa in the home setting by a visiting nurse. Specifically, no patient experienced the new onset of	All patients received intravenous infusions of agalsidase alfa (0.2 mg/kg) administered every other week over a 40 min period during the entire duration of the open-label study	none	4–4.5 year study	The main outcome measures were safety, antibody response and renal glomerular filtration rate (GFR). With the exception of infusion-related reactions, no serious or non-serious adverse events related to agalsidase alfa therapy occurred. • Eight patients developed persistent IgG antibodies to agalsidase alfa, but IgE antibodies were not detected in any patient. • Estimated GFR remained stable in subgroups of patients with Stage I (GFR >90 ml/min) or Stage II (GFR 60–89 ml/min) chronic kidney disease at baseline. In contrast, in the subgroup of patients with Stage III chronic kidney disease (GFR 30–59 ml/min), the slope of the decline in GFR was reduced compared with comparable historical controls enzyme replacement therapy was slowing the decline of renal function

Bibliographic/citation	Study type	LE	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size
				infusion reactions after switching to home therapy.				
5. William R. Wilcox, Maryam Banikazemi Long-Term Safety and Efficacy of Enzyme Replacement Therapy for Fabry Disease Am. J. Hum. Genet. 75:65–74, 2004	58 patients who participated in the phase 3 doubleblind, randomized, and placebo-controlled trial enrolled in the open-label extension study.	1c	58 patients	58 patients who participated in the phase 3 doubleblind, randomized, and placebo-controlled trial enrolled in the open-label extension study. eight patients had withdrawn (4 patients -voluntary withdrawal, 3 patient withdrawn due to protocol-specified criteria , and 1 patient died). Three patients, who were withdrawn by protocol, had a positive serum IgE or skin test.	all patients received 1 mg/kg (0.9–1.1 mg/kg) of agalsidase beta every 2 wk. Prior to infusion, patients received 500–1,000 mg of acetaminophen. Also, some patients were pretreated with an antihistamine approved by the investigator. A few patients received ibuprofen, prednisone, or both, as pretreatment to minimize infusion-associated reactions (IARs).	none	30 months	• Continuously normal mean plasma globotriaosylceramide (GL-3) levels during 30 months of the extension study • the sustained capillary endothelial GL-3 clearance in 98% (39/40) of patients who had a skin biopsy taken after treatment for • 30 mo (original placebo group) or 36 mo (original enzyme-treated group). The mean serum creatinine level and estimated glomerular filtration rate also remained stable after 30–36 mo of treatment. Infusion-associated reactions decreased over time, as did anti-rh-aGalA IgG antibody titers
6. M Connock,1 A Juarez-GarciaA systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type 1 *Health Technology Assessment* 2006; Vol. 10: No. 20	Systematic Reviews	1			Fabrazyme, Replagal or human agalsidase alfa			• The results suggested beneficial effects of ERT on measures of pain, cardiovascular function and some end-points reflecting neurosensory function. • Renal function appeared to be stabilised by ERT. • The mean cost per patient (50 kg) treated is approximately £85,000 per annum in England and Wales. The cost per patient varies considerably by dose. • *Cost per quality-adjusted life-year:* ERT was assumed to restore patients to full health in the base case. • The estimated incremental cost-effectiveness ratio (ICER) in the base case was £252,000 per QALY (Fabrazyme). • the authors of this report recommend the establishment of disease specific data registries which attempt to include all affected patients in the

Bibliographic/citation	Study type	LE	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size
								UK, and collect longitudinal patient level data on clinically relevant problems, interventions received and quality of life in a utility format Data from registries should be readily accessible (in anonymised form) to facilitate the process of technology assessment and improving patient care
7. Mignani R, Panichi V, Giudicissi A, et al. Enzyme replacement therapy with agalsidase beta in kidney transplant patients with Fabry disease: a pilot study. Kidney Int. 2004. 65: 1381-85.	Case series Aim: To assess the safety and efficacy of ERT with recombinant human-α-galactosidase A in kidney transplant recipients with Fabry Disease	4	n= 3	Male kidney patient transplant recipients with biocechemically, genetically and histologically confirmed Fabry disease.	Recombinant human-α-galactosidase A algasidase beta (1 mg/kg body weight 2 weeks IV for 18 months)	none	18 months	Outcome measures: • Cardiologic evaluation - echocardiography by same operator at 1st, 12th and 18th months Biochemical evaluation – Gb_3 conc. in plasma and urine. **Results:** **Efficacy** - extremity pain and paresthesias in the patient - it disappeared within 2 months. - Serum creatinine remains stable for all 3 pts. - In pt with proteinuria, resolved after 10 months of ERT. - Pt with atrial fibrilation persisted. *Inconsistent response in Cardiologic evaluation.* **Safety:** - 2 patients tolerated it well with 1 pt experience an episode of gasteroenteritis- however attributed to viral infection. ERT stop for 5 months and reintroduced without complications **Outcome measures not consistent with results reported. The aim was not suitable with the study design . It can only describe not assess the safety and efficacy.**
8. Raphael S, Jeffrey K, Howard A, et al. Enzyme Replacement Therapy in Fabry Disease: A Randomized Controlled Trial. JAMA 2001; 285(21): 2743 -2749	Randomized control trial (double blinded)	1b	26 patients Group 1 n=14 (ERT) group 2 n=12 (control)	26 hemizygous men age 18 and above with Fabry disease confirm by [alpha]-gal A assay (all patient had neuropathic pain)	[alpha]-Gal A (0.2 mg/kg) IV infusion. (Fully human prep.) [initially 20 min. Approx. midway time increased to 40 min to diminish the likelihood of mild infusion reactions] (Doses every other week for 6 months (12	Placebo infusions, {aside from the absence of [alpha]-gal A, placebo were identical to the enzyme infusions in composition, appearance, and method of administration	24 weeks	Outcome measures: • **Neuropathic pain**. The primary efficacy end point was the effect of therapy on neuropathic while without pain medications. *Results:* Pain at its worst decline in treatment gp. Overall pain score - a significant decline in treatment gp(p=.02). Pain related QoL improved (p=.05). 4 of the treated were able to discontinue taking pain medication and none in placebo gp. (The level of **Neuropathic pain** decreased approx. 2 units on BPI (1 unit is considered clinically significant) **The pain related QoL** as measured by interference items in BPI)

Bibliographic/citation	Study type	LE	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size

					doses total			• **Renal Outcome**. Glomerular filtration rate and renal biopsy-consensus score reached. *Results;* Intervention was associated with:
								  o 1) Improvement in glomerular histology (fraction of normal glomeruli and mesangial widening) but no significant change in total score for tubulointerstitial pathology.
								  o 2) Creatine clearance improve in treatment gp (2.1 mL/min/1.73 m^2 p=.02) but in placebo gp worsen. Inulin clearance greater decrease in placebo gp but not statistically significant (p=0.19).
								• **Gb_3 Analysis. Level** of Gb_3 in plasma, 24-hr urine sediment and in renal biopsy tissue. *Result;*
								  o 1) Decrease in the plasma Gb_3 levels by 6.56 nmol/mL and 0.77 nmol/mL (p=0.005) in intervention and placebo gp respectively.
								  o 2) The 24-hr urine Gb_3 sediment levels decrease by 686 nmol/g creatinine in intervention gp and increase by 333 nmol/g creatinine (p=.05) in placebo gp.
								  o 3) The renal biopsy Gb_3 level decrease by 4.0 and 0.9 nmol/mg in intervention and placebo gps respectively (p=0.27)
								Safety
								  o 8/14- reported mild infusion reactions, generally consisting of rigors within 45 minutes following infusion which were readily controlled with antihistamines and low dose corticosteroids.
								  o Reduce infusion rate resulted in no patients developing IgE, IgA or IgM antibody to [alpha]-Gal A.
								  o 3/14 patients in intervention gp developed low-titre (1:10) IgG antibody.
								  o 9/14 +ve by immunoprecipitation assay (titre 1:2), the presence of antibodies did not correlate with incidence of infusion reactions.
								  o

9. Moore, David F., Ries, Markus, Forget, Evelyn L. Schiffmann, Raphael (2007) Enzyme Replacement Therapy in Orphan and Ultra-Orphan Diseases: The Limitations of Standard Economic Metrics as	Expert opinion			search Use limited quality of life (QOL) data available in the Fabry-Anderson disease literature on ERT to derive				ERT for Fabry-Anderson disease is not economically viable by standard health programme evaluation metrics. Base on ERT costs (year 2005 values), derivation of the INB (incremental net benefit) distribution, and a Bayesian analysis using an enthusiastic and skeptical prior of the INB, an upper ($US350,00 over 1 year) and lower ($US175,000 over 1 year) economic cost, respectively, of ERT was derived.

Bibliographic/citation	Study type	LE	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size
Exemplified by Fabry-Anderson Disease PharmacoEconomics, (25)3:201-208(8)				standard economic metrics.				

Evidence table: Pompe disease
Question: Is Enzyme Replacement Therapy in Pompe disease safe, effective and cost effective.

Bibliographic citation	Study type	LE	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size
1. Johanna M.P. Van den Hout, Joep H.J. Kamphoven et al. Long-Term Intravenous Treatment of Pompe Disease With Recombinant Human _-Glucosidase From Milk.. Paediatrics Vol. 113 No. 5 May 2004	The study was a single-center, open-label, phase II study approved by the institutional review boardThe objective of the study was to evaluate the safety and efficacy of rhAGLU. A line of transgenic rabbits producing rhAGLU was obtained. Rabbit milk was collected and stored at -20°C until use	1c		Patients qualified for inclusion when they had symptoms characteristic of the infantile form of Pompe disease, including a hypertrophic cardiomyopathy. The upper age limit was 10months. Confirmation of the diagnosis was required by an open biopsy from the quadriceps muscle, revealing a virtual absence of α-glucosidase activity and the presence of lysosomal glycogen storage. The α-glucosidase activity in skeletal muscle and fibroblasts of all 4 patients was below the lower limit of detection (_2% of Normal) The 95-, 76-, and 70-kDa biosynthetic forms of α-glucosidase were missing in 3 of the 4 patients,	After intermediate purification on a Phenyl Sepharose HP column α-glucosidase was polished by Source Phenyl 15 chromatography After a second viral removal step by nanofiltration,purified α--glucosidase was concentrated by ultrafiltration (Biomax 30 membrane) and sterilized by microfiltration The enzyme has a specific activity of 250 µmol/ mg/hour for 4 methylumbelliferyl-α-D-glucopyranoside and is >95% pure RhAGLU was administered intravenously as a 1- to 2-mg/mL solution in saline with 5% glucose and 0.1% human serum albumin,in single starting doses of 20 mg/kg weekly for patients <6.5kg and 15 mg/kg for patients >6.5 kg. After 14 to 23 weeks of treatment, the dose was increased to 40 mg/kg weekly for all infants		22 months	• During the first 12 weeks of treatment, muscle α-glucosidase activity increased from <2% to 10% to 20% of normal in all patients. The rhAGLU dose in all infants was increased to 40 mg/kg, and this resulted,12 weeks later, in normal α-glucosidase activity levels • Twelve weeks after dose elevation, signs of muscle regeneration in 3 of the 4 patients was seen. • All 4 patients had the characteristic cardiac hypertrophy at start of treatmentDuring 84 weeks of treatment, the LVMI decreased from 171, 203, 308, and 599 g/m2 at baseline to 70, 160, 104, and 115 g/m2 for patients 1, 2, 3, and 4, respectively • progress in motor development was seen in the younger patients (patients 1and 3) Patient 1 learned to crawl (12 months),walk (16 months), squat (18 months), and climb stairs(22 months). Patient 3 learned to sit unsupported, and her condition further improved until the ageof 2, when she became ventilator dependent. • Three of the 4 patients are alive. All 4 patients reached the age of 4 years, whereas the life expectancy of untreated patients with the classic infantile form of Pompe disease is typically <1 year

Bibliographic citation	Study type	LE	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size
2) J. M. P. Van Den Houti, A. J. J. Reuser et al Enzyme therapy for Pompe disease with recombinant human a-glucosidase from rabbit milk. J. Inherit. Metab. Dis. 24 (2001) 266-274	single-centre, open-label pilot study Muscle biopsies were scheduled at baseline and subsequently at 12-week intervals to assess uptake of a-glucosidase and changes in histopathology. Biopsies were taken from the quadriceps muscle via an open muscle biopsy, one day after infusion of recombinant human α-glucosidase	1c	4	Four patients with infantile Pompe disease	The recombinant α-glucosidase that was used in the study is produced in transgenic rabbits by the epithelial cells of the mammary gland. As a result of testing and selective breeding, a line of rabbits was obtained producing recombinant human α-glucosidase (rhAGLU) during lactation. rhAGLU is extracted from the milk by multistep column chromatography and mixed with infusion fuid for intravenous administration		12 mnths	**Uptake of a-glucosidase by muscle:** • Twelve weeks after treatment (t.-1) with weekly dose of 15 or 20 mg/kg, a second biopsy was taken. A 7^30-fold increase of a-glucosidase activity in muscle was seen, demonstrating that the target tissue was reached. • the dose of all patients were increased to 40 mg/kg weekly. Twelve weeks thereafter(t- 2.) another biopsy was taken All patients had now acquired normal α-glucosidase activities **Histopathology:** • Twelve weeks after dose increase, a signi¢cant reduction of PAS-positive material was observed but the total tissue glycogen content had not changed signi¢cantly. **Clinical ¢ndings** • The late-included patients had the poorest motor condition at the start of treatment.They were able to lift their arms only brie£y, while their legs lay £at on the surfacein a frog-like position without any movement. During the 36 weeks of treatment, the patients gained strength in their arms. They learned to play with toys above their head and to transfer objects. Head balance improved slightly. • The best effect was seen in the two patients who were included early. At 36 weeks of treatment, the younger of the two could lift her legs freely from the surface and had learned to touch her feet in play. She turned her upper body completely, but was not ableto roll over. • Patient 1 who had the best motor condition at start of treatment, has shown the most remarkable progress. At 9.5months of age he learned to sit independently without arm support and at 10 months he started to crawl. At 11 months he pulled to a standing position and cruised along furniture. At 12 months, he learned to crawl in a four-point position and to stand with support of one arm. **Heart:** All patients had a cardiomegaly at the start of treatment, characteristic for infantile Pompe disease The two best-performing patients in the study each had a cardiomegaly at birth. The left ventricular mass index and left ventricular posterior wall thickness decreased signi¢cantly after start of treatment with rhAGLU (Van den Hout et al 2000). The largest reduction was seen in patient 4. At 36 weeks of treatment the LVMI had decreased to 30% of the baseline value. Both the atelectasis of the left lung and the signs of cardiacinstability had disappeared. The combined effects of rhAGLU were life saving for this patient

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Bibliographic citation	Study type	LE	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size
3) Amalfitano A, Bengur AR, Morse RP, Majure JM, Case LE, Veerling DL, et al. Recombinant human acid alpha-glucosidase enzyme therapy for infantile glycogen storage disease type II: results of a phase I/II clinical trial. Genet Med 2001;3:132-8.	In a parallel phase I/II trial,	1c	3 infants	3 infants	twice-weekly infusions of recombinant human GAA manufactured in a Chinese hamster ovary cell line			Heart size decreased and cardiac function remained normal, and glycogen deposits in skeletal muscle decreased markedly in one patient. All infants in both studies survived past the critical age of 1 year
4) Kishnani P, Voit T, Nicolino M, Tsai C-H, Herman G, Waterson J, et al. Enzyme replacement therapy with recombinant human acid alpha glucosidase (rhGAA) in infantile Pompe disease (IPD): results from a phase 2 study. [abstract]. Pediatr Res 2003;53:259.	open-label phase II study	1c	8 infants	eight infants with infantile-onset Pompe disease and cardiomegaly and cardiomyopathy by age 6 months	Chinese hamster ovary cell-derived recombinant human GAA			Three infants died of complications of their disease. Four of the five surviving infants are ventilator-free. All five infants have shown motor improvement; three are now ambulatory with normal motor development, whereas the remaining two have shown modest motor improvement. After≥12 months of treatment, all five have a markedly decreased left ventricular mass index and normal Bayley mental development index.

Bibliographic citation	Study type	LE	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size
5) Van Der Ploeg, A Reuser and C Van cappelle. Early signs of benefit in children with late-onset Pompe Disease following the first 6 months of treatment with enzyme replacement therapy with the recombinant human acid alpha glucosidase (rhGAA) in an open –label study. Presented at 2006 Annual Clinical Genetics Meeting, American college of medical genetics; March 23-26 2006, san Diego, CA (abstract}	Open label study	1c	5 patints – 3male and 3 females	5 caucasian patients aged 5-15 years with late-onset pompe disease	rhGAA (20 mg/kg IV)			Clinically meaningful increase in percent predicted forced vital capacity (increase in FVC > 11%) in 3 patients (2 had FVC <80% at baseline) after 6 months treatment. Also an increase in the 6 minute walk test conducted at fast speed (increase in distance walked > 37 metres) in 3 patients
6) Van der Ploeg A. Response to enzyme replacement therapy in 18 juvenile and adult patients with severe Pompe disease. 59th Annual Meeting of the American Academy of Neurology, Apr 28- may 5 2007 (abstract)	Clinical trial or compassionate program	1c	18 patients	Juvenile and adult patients with severe pompe disease.	10 mg / kg weekly or 20 mg/kg biweekly myozyme ERT infusions.		6 months	At baseline all patients were wheelchair bound. 10 of 17 patients demonstrated improvements in respiratory function, including a 50% reduction in required ventilation for one patient. Motor function improved for 13 of 18 patients, and stabilized in the remaining 5 patients; no declines in muscle strength or tone were noted. Almost all 15/16 patients reported improvements in their quality of life since commencing ERT.

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Bibliographic citation	Study type	LE	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size
7) Ravaglia S, DanesinoC Rissi M et al. enzyme replacement therapy (ERT) in adult-onset type II glycogenesis (GSDII). 59th Annual Meeting of the American Academy of Neurology, Apr 28- may 5 2007 (abstract)	Open label trial	1c	6 DSDII patient	Aged 58 +/- 13.3 years with severe respiratory failure and moderate to severe limb girdle involvement. All patients carried the IVS1 (-13T-G) mutation	20 mg/kg every 2 weeks of myozyme – genzyme started between July 2005 and March 2006 and been continued to Oktober 2006		1 year	In 4/5 patients the respiratory function improved, up to 100% of basal value in the patient with the longest follow-up (1 year). MMT scor improved in pelvic muscles in 3/5 patients and in leg and thigh muscle in all patients. Muscle MRI showed increased muscle bulk.
8) D. Lianu, D. Syrengelas, P. Poulopoulos et al. Early signs of benefit in a child with late-onset Pompe disease following treatment with enzyme replacement therapy. Presented at the fourth symposium on lysosomal storage disorders; mar 29-31, 2007; Vienna, Austria. (abstract)	Case study	4	1 patient	A patient with juvenile – onset pompe disease	Myozyme 20 mg / kg		10 months	A subtle improvement of skeletal muscle strength and function was noted. The GMFM score (dimension E : walking, running, jumping) improved from 95.8% to 98.6% and the HHD score increased from 1,262 to 1,404 newton.
9) Mathias spranger, Birgit Grunet et al. Clinical course of seven patients with late-onset Pompe disease on enzyme replacement therapy. Presented at the fourth symposium on lysosomal storage disorders; mar 29-31, 2007; Vienna, Austria. (abstract)	Case series	4	7 patients (5 males and 2 females)	Aged 23 and 68 years with adult pompe disease	Intravenous myozyme every 14 days for 6 to 9 months.		6-9 months	All patients were monitored by dyamometer, timed tests (10 m-walk, 6 min-walk, stand up and go-test, climbing chairs, a treadmill test) and the Medical Research Council (MRC) score. Activity was measured by the Functional Independence Measure (FIM) and participation by the SF-36 questionnaire. Muscle strength improved in all patients but one by 5 to 15 % . Timed test improved in all but ne by 13 to 50%. FIM –score (by 5 t 11%) and participation improved in all patients but one.

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Bibliographic citation	Study type	LE	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size
10) Klinge L, Straub V, Neudorf U, Schaper J, Bosbach T, Görlinger K, Wallot M, Richards S, Voit T.Safety and efficacy of recombinant acid alpha-glucosidase (rhGAA) in patients with classical infantile Pompe disease: results of a phase II clinical trial Neuromuscul Disord. 2005 Jan;15(1):24-31. Epub 2004 Nov 26	phase II clinical trial	1c	two patients with classical infantile Pompe disease		Recombinant acid alpha-glucosidase was derived from the milk of transgenic rabbits. enzyme replacement therapy over a period of 48 weeks by weekly infusions		48 weeks	Safety was evaluated by recording adverse events while clinical efficacy was evaluated by ventilator-free survival, left ventricular mass index, motor development as well as histologic and biochemical analysis of muscle biopsies. This therapy was in general well-tolerated. There was an overall improvement in left ventricular mass, cardiac function, skeletal muscle function and histological appearance of skeletal muscle.
11) Klinge L, Straub V, Neudorf U, Voit T. Enzyme replacement therapy in classical infantile pompe disease: results of a ten-month follow-up study. Neuropediatrics. 2005 Feb;36(1):6-11	Case series	4	2 children with Infantile Pompe disease (IPD) who previously completed a 48-week course of enzyme replacement therapy (ERT) with the same medication at the same dose in a phase II clinical trial.		recombinant human precursor acid alpha-glucosidase (rhGAA		10 months	Under this therapy cardiac status and muscle strength had improved, leading to survival beyond the age of one year. These results, together with data from two other phase II clinical trials encouraged further evaluation of the long-term safety and efficacy of enzyme replacement therapy in patients with infantile-onset Pompe disease. During the 10-month follow-up period, ERT was well-tolerated and neither patient experienced a single infusion-associated reaction. The initial improvements in cardiac size and function, as measured by left ventricular mass index and the fractional shortening, were maintained in both patients, and a continued improvement of motor function, as measured by the Alberta infant motor scale, was observed.

APPENDIX 4

The following are the results of search on the burden of disease, treatment and cost effectiveness:

Key words	2007	2006	2005	2004	2003	2002	2001	total
enzyme replacement therapy	280	86	773	462	315	347	374	2637
enzyme replacement therapy for gaucher disease	19	57	27	25	37	34	31	230
enzyme replacement therapy for fabry disease	40	61	55	39	35	40	18	288
enzyme replacement therapy for pompe disease	16	21	11	39	7	5	4	71
Cost effectiveness of enzyme replacement therapy	2	4	3	1	1	1	4	16
Strategies for enzyme replacement therapy	16	35	4	22	12	29	20	138
Cost of enzyme replacement therapy	6	16	7	10	5	11	8	63
Models for enzyme replacement therapy	41	38	64	58	51	42	36	330
Policy on enzyme replacement therapy	1	4	2	-	-	1	1	9
Prevalence and incidence of gaucher disease	9	21	9	12	12	17	13	93
Prevalence and incidence of fabry disease	21	23	29	19	21	13	12	138
Prevalence and incidence of pompe disease	5	3	2	-	2	2	1	15