Enzym Replacement Therapy for Lysosomal Storage Diseases

Final Report

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1 Introduction and background

Lysosomal storage diseases (LSD) are a heterogenous group of more than 40 inborn errors of metabolism that are due to specific defects of lysosomal enzymes, lysosomal membrane proteins or transporters respectively. All LSD are inherited autosomal recessively with the exception of MPS II (M. Hunter), Fabry Disease and Danon Disease that are inherited as X chromosomal traits. Although individually rare their cumulative prevalence may be as high as 1:800 in certain ethnic populations.

LSD are a heterogenous goup of inborn errors of metabolism …

… which are individually rare

Table 1: Number of patients with LSD worldwide and in Austria

	Number of LSD patients world wide /Austria	Number of treated patients with ERT world wide /Austria
MPS I	3000/3	600/3*
MPS II	2000/10	?/8
MPS VI	1100/1	?/1
Pompe	5000-10000/10	800/9
Fabry	4000-5000/25	220/18
Gaucher	5000-6000 /23	5200/22

** 1xERT + 2xBMT*

LSD in general are progressive multiorgan disorder with about 50% having significant central nervous involvement. Each LSD comprises a more or less unique clinical spectrum with patients at the more severe end showing increased morbidity and mortality whereas patients at the milder end of the spectrum having only subtle clinical signs. Patients with mild disease may often go unrecognized for many years.

progressive multiorgan disorder with different clinical occurrence

Therapy of LSD consisted mainly of palliative treatment until the recent development of enzyme replacement therapies for Gaucher, Pompe and Fabry Diseases as well as Mucopolysaccharidosis types I and II (MPS I/II) [Belani et al. 1993; Burrow et al. 2007].

palliative treatment

ERT

Lysosomes are intracellular organelles that encompass numerous hydrolases and other enzymes that break down different compounds derived from intermediary metabolism such as complex lipids, carbohydrates and others.

lysosomes are intercellular organelles

During the last years the interest for the LSD has significantly increased due to the development of novel therapies including enzyme replacement therapies (ERT) and substrate inhibition therapy. Additional therapies such as chaperone therapy are currently evaluated in phase I and II trials. Currently ERT are available for MPS I, II, VI, Fabry, Pompe and Gaucher diseases. In addition SRT has been licensed for Gaucher disease.

ERT, substrate inhibition therapy, haperone therapy

aim of this paper:

overview of LSD, provide guidelines, summarise data and analyse field of conflict

The aim of this paper is to give a brief overview of the treatable LSD, to summarise the guidelines for diagnosis, treatment and disease management, to summarise data from ERT registers and to analyse eventual fields of conflict. For this purpose a thorough Medline search up to August 2008 was performed using the following key words: MPS I, MPS II, MPS VI, Pompe, Fabry, Gaucher, enzyme replacement therapy, treatment and registry respectively. In addition all pharmaceutical companies involved in manufacturing recombinant enzyme and/or substrate inhibition therapies were contacted for further information. These companies included Actelion, Biomarin, Genzyme and Shire.

*Table 2: Registered enzyme replacement and substrate reduction therapies**

LSD	Trade name (chemical name)/company	Dose/Interval
MPS I	Aldurazyme (Laronidase)/Genzyme/BioMarin	0.5 mg/kg/week
MPS II	Elaprase(Idursulfase)/Shire	0.5 mg/kg/week
MPS VI	Naglazyme (Galsulfase)/BioMarin	1.0 mg/kg/2 weeks
POMPE	Myozyme (Alglucosidase Alfa)/Genzyme	20 mg/kg/2 weeks
FABRY	Replagal (Agalsidase Alfa)/Shire	0.2 mg/kg/2 weeks
	Fabrazyme (Agalsidase Beta)/Genzyme	1.0 mg/kg/2 weeks
GAUCHER	Cerezyme (Imiglucerase)/Genzyme Zavesca (Miglustat)Actelion*	15-60 Units/kg/2 weeks 300 mg/day

2 Mucopolysaccharidosis

MPS are a group of LSD

The MPS are a group of LSD that are caused by the malfunction or absence of the specific lysosomal enzyme that is required for break down of glycosoaminoglycans (GAG) including heparan and dermatan sulphates [Nelson 2001; Wraith et al. 1987]. The overall incidence of MPS is approximately 1 in 25,000 of live births. It is estimated that worldwide 3000 patients suffer from MPS I and 1100 from MPS VI. The actual number of patients with MPS II is unknown. Frequently patients with MPS require surgical interventions due to acute and/or subacute disease related complications. As patients with MPS carry a significant perioperative (anesthetic) risk, they should be only managed at experienced, well-equipped centers [Belani et al. 1993].

Incidence: 1:25000 live births

2.1 Mucopolysaccharidosis type I (MPS I, Hurler Syndrome)

MPS-I is due to deficiency of the intra-lysosomal enzyme α -L-iduronidase that leads to progressive storage of glycosaminoglycans (GAG) in all tissues. The resulting clinical phenotype follows a spectrum with Hurler Syndrome at the severe end, Hurler-Scheie Syndrome as intermediary and Scheie Syndrome at the mild end of the disease spectrum. The incidence of MPS I varies between 1:76,000 newborns (Hurler Syndrome), 1:280,000 newborns (Hurler-Scheie Syndrome) and 1:1.3 million newborns (Scheie Syndrome). The cumulative incidence for all three "subtypes" of MPS I is 1:100,000 newborns. The cumulative prevalence for all three "subtypes" of MPS I is 0.3 per 100,000 inhabitants (United Kingdom). MPS I may be more frequent in different ethnic populations. MPS I is inherited as an autosomal recessive trait carrying a 25% recurrence risk for future pregnancies.

cumulative incidence: 1:100,000 newborns

2.1.1 Clinical symptoms

Hurler Syndrome:

clinical symptoms present at birth; develop durging 1st year of life

Clinical symptoms may be already present at birth in patients with Hurler Syndrome but typically develop during the first year of life. Symptoms may include coarse facial features, hepatosplenomegaly, cardiomyopathy, macrocephaly, hydrocephalus, obstructive airway disease, gibbus, restricted joint movement and recurrent infections of the upper airways and middle ears. Early psychomotor development may be normal but may be significantly delayed at 1-2 years of age. Patients with Hurler Syndrome, when left untreated rapidly progresses afterwards and leads to death during the second decade of life [Cleary et al. 1995].

Hurler-Scheie Syndrome

onset of symptoms between 3 and 8 years

siagnosed much later

Onset of symptoms in patients with Hurler-Scheie Syndrome is typically between 3 and 8 years of age but most patients are diagnosed much later. Importantly, Central Nervous System (CNS) involvement is less frequent and/or less severe, although expectancy of life may be reduced due to cardiac and pulmonary involvement. In contrast patients with Scheie Syndrome have a much later onset of very mild symptoms and are frequently not diagnosed accordingly.

2.1.2 Diagnosis

diagnosis: in leukocytes or dry blood spots

Diagnosis of MPS I is based on demonstration of deficiency of α -L-iduronidase in either leukocytes or dry blood spots, the latter with the potential for eventual newborn screening. In addition the biochemical analysis of urinary GAG may help to raise the suspicion for MPS I. Mutation analysis is used for confirmatory diagnosis and prenatal diagnosis respectively.

2.1.3 Therapy

mainstay of therapy: BMT or SCM

Mainstay of therapy for patients with Hurler Syndrome is bone marrow or stem cell transplantation (BMT or SCM). The best outcome is obtained when transplantation is done before 2 years of age. In addition recombinant enzyme (Laronidase/Aldurazyme®) manufactured by Genzyme and Biomarin for enzyme replacement therapy of all "subtypes" of MPS I was registered and approved by FDA in 2003 and EMEA in 2004 [Kakkis et al. 2001; Thomas et al. 2006; Wraith et al. 2004].

published treatment guidelines

The only treatment guidelines published to date can be found under the following weblink: www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4118402 [Wraith et al. 2005].

2.2 Mucopolysaccharidosis type II (MPS II, Hunter Syndrome)

incidence varies between 1:65,000 and 1:132,000

MPS-II is due to deficiency of the intra-lysosomal enzyme α -L-iduronate sulphatase that leads to progressive storage of glycosaminoglycans (GAG) in all tissues. The incidence of MPS II varies between 1:65,000 and 1:132,000 newborns. The prevalence for MPS II is 0.67 per 100,000 inhabitants (United Kingdom). MPS II may be more frequent in different ethnic populations.

2.2.1 Clinical symptoms

clinical symptoms typically develop during first years of life

Clinical symptoms may be already present at birth in some patients with Hunter Syndrome but typically develop during the first years of life. Symptoms may include coarse facial features, hepatosplenomegaly, cardiomyopathy, macrocephaly, hydrocephalus, obstructive airway disease, gibbus, restricted joint movement and recurrent infections of the upper airways and middle ears. Early psychomotor development may be normal but may be significantly delayed at 1-2 years of age in a subgroup of patients with CNS involvement. Patients with the severe form of MPS II when left untreated rapidly progresses afterwards and leads to death during the second decade of life. In contrast patients with a milder form of MPS II have a much later onset of symptoms.

severe form when left untreated: rapid progress

milder form: later onset of symptoms

2.2.2 Diagnosis

Diagnosis of MPS II is based on demonstration of deficiency of α -L-iduronate sulphatase in either leukocytes or dry blood spots, the latter with the potential for eventual newborn screening. In addition the biochemical analysis of urinary GAG may help to raise the suspicion for MPS II. Mutation analysis is used for confirmatory diagnosis and prenatal diagnosis respectively.

diagnosis: leukocytes or dry blood spots

2.2.3 Therapy

Recombinant enzyme (Idursulfase/Elaprase®) manufactured by Shire for enzyme replacement therapy of MPS II was registered and approved by FDA in 2003 and EMEA in 2004 [Muenzer et al. 2006]. The only treatment guidelines published to date can be found under the following weblink: www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_073341
[Vellodi et al 2007]. Home treatment has been demonstrated to be safe in patients with MPS II and MPS VI [Bagewadi et al. 2008].

ERT

safe home treatment in patients with MPS II and MPS VI

2.3 Mucopolysaccharidosis type VI (MPS VI, Maroteaux Lamy Syndrome)

MPS-VI is due to deficiency of the intra-lysosomal enzyme N-acetylgalactosamine-4-sulphatase (arylsulphatase B) that leads to progressive storage of glycosaminoglycans (GAG) in all tissues. The estimated incidence of MPS VI is 1:235,000 newborns. The prevalence for MPS VI is 0.23 per 100,000 inhabitants. MPS VI may be more frequent in different ethnic populations.

incidence: 1:235,000 newborns

2.3.1 Clinical symptoms

Clinical symptoms may be already present during the first year of life, but patients with MPS VI are typically brought to medical attention at 2 to 3 years of age for evaluation of short stature. At that time the patients may also have coarse facial features, skeletal abnormalities including bone deformities, hepatosplenomegaly and inguinal hernias. Typically, intellectual impairment is not observed [Azevedo et al. 2004].

clinical symptoms present during fist year of live

medical attention at 2 to 3 years of age

2.3.2 Diagnosis

Diagnosis of MPS VI is based on demonstration of deficiency of N-acetylgalactosamine-4-sulphatase (arylsulphatase B) in leukocytes. In addition the biochemical analysis of urinary GAG may help to raise the suspicion for MPS VI. Mutation analysis is used for confirmatory diagnosis and prenatal diagnosis respectively.

diagnosis: in leukocytes

2.3.3 Therapy

ERT

Recombinant enzyme (Galsulfase/Naglazyme®) manufactured by Biomarin for enzyme replacement therapy of MPS VI was registered and approved by FDA in 2005 and EMEA in 2006 [Harmatz et al. 2006]. Bone marrow transplantation has been done in single patients with MPS VI with limited benefit. Management guidelines for patients with MPS VI have been recently published [Guigliani et al. 2007]. Home treatment has been demonstrated to be safe in patients with MPS II and MPS VI [Bagewadi et al. 2008].

BMT with limited benefit

2.4 Pompe Disease (Glycogen Storage Disease Type II (GSD-II)

infantile-onset vs. adult-onset phenotype

Pompe Disease (PD) is due to intra-lysosomal storage of glycogen secondary to deficiency of acid α-glucosidase (GAA). The resulting clinical phenotype comprises a clinical spectrum with the infantile-onset phenotype at the severe end and the adult-onset phenotype at the mild end of the disease spectrum.

2.4.1 Clinical symptoms

variable albeit progressive intra-lysosomal glycogen storrage in skeletal musclues, heart and smooth muscles

All patients with PD have a variable albeit progressive intra-lysosomal glycogen storage in skeletal muscles, heart and smooth muscles with resulting organ damage and ultimate organ failure. The rate of glycogen accumulation depends on residual enzyme activity, environmental factors (nutrition), physical activity and yet unkown genetic modifier. Patients with the same haplotypes may in fact exhibit different clinical phenotypes.

2 categories of PD:

infantile onset and late-onset

PD is classified into two separate categories - infantile-onset and late-onset - based on age of onset of symptoms, although there may be significant overlap between the two. It is preferred to view the clinical phenotype of PD as clinical disease spectrum similarly to other inborn errors of metabolism with a severe and a mild end of the clinical spectrum based on severity of clinical symptoms in relation to age of onset.

2.4.2 Infantile-onset PD

patients usually die within the first year of life due to cardorespiratory failure

Patients with infantile-onset („classic“) PD present with progressive left ventricular hypertrophy and generalised muscular hypotonia („floppy infant“) and typically die within the first year of life due to cardio-respiratory failure. Significant cardiomyopathy may already be present in-utero and readily detected by prenatal ultrasound. In addition electrocardiogramm may show conduction abnormalities including short PR intervals and tall QRS complexes as well as Wolf-Parkinson-White syndrome in some patients. Additional symptoms include macroglossia, heptomegaly, splenomegaly and feeding difficulties. Data from more than 150 patients with infantile-onset PD revealed a median age at first symptoms from 1.6 to 2 months and the median age of death from 6.0 to 8.7 months [Di Rocco et al. 2007; Kishnani et al. 2006a].

neurological symptoms not readily observed

Neurological symptoms in infantile-onset PD are not readily observed due to early death within the first year. The advent of enzyme replacement therapy and the increased survival rate in infants treated early have uncovered neurological manifestions of PD related to cochlear dysfunction and delayed myelination respectively, that have not been reported previously [Chien et al. 2006]. Involvement of the central and peripheral nervous systems is due to progressive storage of glycogen.

2.4.3 Late-onset PD

clinical symptoms: progressive muscle weakness …

… and occasionally respiratory failure

The leading clinical symptom in patients with late-onset PD („non-classic", childhood, juvenile or adult-onset) is progressive muscle weakness due to initial involvement of the muscles of the proximal lower limbs and the paraspinal muscles. Additional involvement of the diaphragm and accessory respiratory muscles may eventually lead to respiratory failure necessitating assisted ventilation even when patients are still ambulatory. Occassionally respiratory failure may be the presenting clinical symptom associated with frequent upper airway infections, orthopnea, sleep apnea and morning headaches [Ausems et al. 1999]. Cardiac involvement is typically not oberved in late-onset PD [Di Rocco et al. 2007; Lafore et al. 2001].

Vascular involvement of large intracranial blood vessels due to glycogen storage in vascular smooth muscle cells leading to cerebral aneurysmata has been reported in single patients.

2.4.4 Diagnosis

biochemical diagnosis in leukocytes or dry blood

Serum creatine kinase, transaminases and LDH are typically elevated in any patient with PD, but may be occasionally within normal limits in single patients with adult-onset PD. Diagnosis of PD should be sought biochemically in leukocytes or dry blood [Kallwass et al. 2007]. Muscle biopsies for primary diagnostic purposes are obsolete as the false negative diagnostic rate may be significant [Kishnani et al. 2006c].

2.4.5 Therapy

individual response to ERT varies due to development of rhGAA specific antibodies, age of presentation and progression of disease

Alglucosidase alfa (recombinant GAA (rhGAA), Myozyme®) has been shown to be effective in the treatment of patients with early and late-onset PD [Amalfitano et al. 2001; Geel et al. 2007; Kishnani et al. 2006c]. The individual response to enzyme replacement therapy may vary due to development of rhGAA specific antibodies, age of presentation and progression of disease. The development of rhGAA antibodies may be more frequent in patients with absent GAA protein or cross-reacting immunological material (CRIM). The absence of CRIM (CRIM negative) may have an impact on the prognosis of patients with infantile onset PD. So far induction of immune tolerance to reduce rhGAA antibody formation has only been evaluated in GAA knockout mice, but to our knowledge not in any patients with PD [Joseph et al. 2008; Sun et al. 2007]. Treatment guidelines for PD have been recently published [Kishnani et al 2006b].

2.5 Fabry disease (FD)

incidence: 1:40,000 newborns

Fabry disease (FD) is due to deficiency of the intra-lysosomal enzyme α -galactosidase A that leads to progressive storage of globotriaosyl ceramide (GL-3) in endothelium and renal podocytes. The estimated incidence of FD is 1:40,000 newborns, although recent studies have demonstrated an incidence as high as 1:3,500 male newborns [Spada et al. 2006]. FD is inherited as a X-chromosomal trait, although both females and males with FD are almost at an equivalent risk of developing severe symptoms.

2.5.1 Clinical symptoms

renal insufficiency, cerebro-vascular events

Clincial symptoms are related to progressive storage of GL-3 in vascular endothelium in various organs including central and peripheral nervous system, heart, kidneys, eyes among others. In classical FD affected individuals may show first symptoms such as acroparesthesia of fingers/toes, chronic diarrhea and angiokeratomata respectively, as early as 10 years of age [MacDermot et al. 2001; Ramaswami et al. 2006; Ries et al. 2005; Ries et al. 2003]. In most individuals with classic FD both males and females renal insufficiency develops eventually. In addition patients with FD are at increased risk for cerebro-vascular events including stroke [Rolfs et al. 2005]. Cardiomyopathy may be the only manifestation of patients with atypical FD [MacDermot et al. 2001; Senechal et al. 2003].

2.5.2 Diagnosis

biochemical diagnosis in leukocytes and/or dry blood spots

Diagnosis of FD is based on demonstration of deficiency of α -galactosidase A in leukocytes and/or dry blood spots. Enzyme analysis in dry blood spots may be used for newborn screening. It should be noted that not all affected females are readily diagnosed due to normal enzyme activity from the non-mutant X chromosome. In these cases mutation analysis may be the preferred method for diagnosis. In addition the biochemical analysis of urinary GL-3 may help to raise the suspicion for FD Mutation analysis is the gold standard and may be used for confirmatory diagnosis and prenatal diagnosis respectively.

gold standard: Mutation analysis

2.5.3 Therapy

ERT approved by the FDA and by EMEA

Recombinant enzyme replacement therapy for the treatment of FD was approved by the FDA in 2003 (agalsidase β/Fabrazyme® by Genzyme) and by EMEA in 2004 (agalsidase β/Fabrazyme® by Genzyme and agalsidase α /Replagal® by Shire) [Ries et al. 2006].

successful home therapy in several countries

Home therapy is done successfully in different countries including the Netherlands and the United Kingdom for several years [Cousins et al. 2008; Linthorst et al. 2006]. There have been several reports regarding treatment guidelines [Desnick et al. 2003; Eng et al. 2006; Ortiz et al. 2008].

2.6 Gaucher disease (GD I)

Gaucher disease (GD) is due to deficiency of the intra-lysosomal enzyme glucocerebrosidase that leads to progressive storage of glucosylceramide in different organs including CNS, liver, spleen, bone marrow and bone. Depending on the presence or absence of CNS involvement different types of GD are distinguished: GD I –non neuronopathic GD, GD II – acute infantile neuronopathic GD, GD III – late neuronopathic GD. The estimated incidence of GD I is 1:57,000 newborns, but may be as high as 1:800 in the Ashkenazi Jewish population. GD is inherited as an autosomal recessive trait [Weinreb et al. 2008; Zimran et al. 1992].

incidence of GD I: 1:57,000

depending of the involvement of CNS different types of GD are distinguished

2.6.1 Clinical symptoms

Patients with GD I may present with anemia, thrombocytopenia, hepatosplenomegaly and symptoms related to bone involvement at any age although most patients present during adulthood. Skeletal symptoms may include bone pain, pathological fractures and bone deformities. There is no intellectual impairment in patients with GD I.

GD I: symptoms occur at any age; usually during adulthood

Patients with GD II may present during their first months of life with hepatosplenomegaly and significant neurological involvement, muscle spasticity and eye movement disorder. Death usually occurs within the first two years of life. Patients with GD III present similarly but during adulthood. Progression of symptoms is much slower.

GD II: symptoms first months of life

GD III: symptoms occur during adulthood.

2.6.2 Diagnosis

Diagnosis of GD is based on demonstration of deficiency of glucocerebrosidase in leukocytes and/or dry blood spots. Enzyme analysis in dry blood spots may be used for newborn screening. In addition chitotriosidase and ferritin levels may be used as biomarker reflecting storage in organs. Mutation analysis is the gold standard and may be used for confirmatory diagnosis and prenatal diagnosis respectively.

biochemical diagnosis in leukocytes and/or dry blood spots

gold standard: Mutation analysis

2.6.3 Therapy

Recombinant enzyme replacement therapy for the treatment of GD was approved by the FDA in 1993 (Imiglucerase/Cerezyme® by Genzyme) [Pastores et al. 1993; Weinreb et al. 2002; Wenstrup et al. 2007]. The first product for ERT has been approved already in early 90's [Barton et al. 1991; Grabowski et al. 1995]. Oral substrate reduction therapy for GD has been approved in 2006 (Miglustat/Zavesca® by Actelion) [Weinreb et al. 2005]. There have been several reports regarding treatment guidelines [Desnick et al. 2003; Eng et al. 2006; Ortiz et al. 2008; Pastores et al. 2004]

ERT approved by FDA

oral substrate reduction therapy

Table 3: Side effects of enzyme replacement therapies

Laronidase/MPS I	Mild to moderate infusion related hypersensitivity reactions: flushing, fever, headache, skin rash
Idursulfase/MPS II	Mild to moderate infusion related hypersensitivity reactions: respiratory distress, hypotension, fever, headache, skin rash, fever, joint pain
Galsulfase/MPS VI	No infusion related reactions reported
Alglucosidase Alfa/ Pompe Disease	Mild to moderate infusion related hypersensitivity reactions: Respiratory distress, hypotension, fever, headache, skin rash, fever. Severity of reaction may not be readily distinguished from the underlying clinical phenotype
Agalsidase Alfa/ Fabry Disease **Agalsidase Beta/ Fabry Disease**	Mild to moderate infusion related hypersensitivity reactions: Respiratory distress, hypotension, fever, headache, skin rash. Mild to moderate infusion related hypersensitivity reactions: Respiratory distress, hypotension, fever, headache, skin rash.
Imiglucerase/ Gaucher Disease	Mild infusion related hypersensitivity reactions.

Table 4: Clinical symptoms of treatable LSD

LSD	MPS I			MPS II		MPS VI	POMPE		FABRY		GAUCHER		
	Hurler	Hurler/Scheie	Scheie	CNS invol.	no CNS invol.		Infantile	Late onset	Classic	Non classic	Typ I	Typ II	Typ III
Coarse facial features	***	***		***	*	***							
Short statute		***		***		***							
Short neck	*												
Sceletal abnormalites	***			***		***					***		
odontoid hypoplasia	***												
Stiffened joints	***	*	***	**	***	***							
Arthrophaty	*												
Distosis multiplex	***	***	*	***	*	***							
Growth delay				***								***	
Developmental regression												***	
Organomegaly													
Hepatosplenomegaly	***	***		***	*	****	***				****	****	****
Cardiomegaly and cardiomyopathy							***	*		*			
Cardiac involment	***	*	***	***	*	***		*	***	***			
Respiratory involment	***	*	*	** +		***			*				*
Frequent respiratory infections						***							
Renal disfunction									***	*			
Urinary incontinence								***					
Cerebrovascular complications									*				
Gastrointenstinal problems									***				
Respiratory insuficiencly							***	***	*				
Cardio Respiratory failure							***						
Thrombocytopenia											***		***
Anemia											***		***
Pancitopenia											***		***
Damaged/affected brain												*	***
Neurological involment												***	***
Intelectual decline		*	*										
Mental retardation	***			***									*
Seizures													***
Peripheral neurophaty	*						***						
Paresthesia and acroparesthesia									***				
Excruciating pain									***				
Progresive muscule weaknees							***	***					
Profound hypotonia							***						
Spasticity												***	
Failure to achieve motor milestones							***						*
Difficulty feeding							***						
Poor cordination													***
Dyshidrosis									*				
Heat/cold intolerance									**				
Angiokeratoma									***				
Corneal clauding	***	***	***			***			***				
Glaucoma	*		*										
Corneal opacity: Cornea verticulata									**				
Ivory-colored skin leasions				***									
Optic atrophy, Retinal degeneration	*		*										
Ptosis								*					
Ocular pinquecule											*		
Eye movement disorder													*
Frequent ear, nose and throat surgery	*												
Vacuolated lymphocites													
Lymphadenopathy													
Dermal hyperpigmentation											*		
Ingvinal umbical hernia	***	***											
GAG(urine) elevated	**	**	**	**	**	**							
Path.Oligosaccharides							***	***			***		
Enzyme studies													
Symptomatic disease(abdominal pain)													
Fatigue											***		
Weight los													
Bone pain											*		
Bleeding											***		
Brusing											*		
Infectious											*		
Hearing los	*			***					***				
Tinitus and vertigo										*			

3 Disease registries

There are company sponsored disease registries including the MPS I registry (Genzyme), HOS (Hunter Outcome Survey, Shire), Fabry registry (Genzyme), FOS (Fabry Outcome Survey, Shire), Gaucher registry (Genzyme) and Pompe registry (Genzyme) respectively. All disease registries are governed by scientific-medical advisory boards at different levels (world-wide and regional) appointed by the respective companies. Members of the scientific-medical advisory boards are typically clinical experts with a long-standing experience in the management of patients with lysosomal storage disorders. A complete list of members of the medical advisory boards can be found on the respective registries homepage (see under websites). A list of treatment centers can be found in table 5, although this list may not be complete as many centers also transfer patients to peripheral satellite clinics. Austria (Olaf A Bodamer) is represented in the Hunter Syndrome Expert Council as well as the MPS I European Advisory Board and all patients with LSD in Austria are included in the respective disease registries.

company sponsored disease registries governed by scientific-medical advisory boards (world-wide/regional)

3.1 MPS I European Advisory Board

The role of the advisory board is to provide expert advice in Europe on all clinical and scientific aspects related to MPS I and the communication to the medical community including management of clinical symptoms and complications, development of severity scores, recommendations for therapy and the use of diagnostic tools. The MPS I European Advisory Board typically meets twice a year.

expert advice on all clinical and scientific aspects related to MPS I

3.2 Hunter Syndrome European Expert Council

The role of the council is to provide expert advice and guidance in Europe on topics such as screening for Hunter syndrome and disease diagnosis, enzyme replacement therapy for patients with severe CNS involvement, ERT for very young patients, moving ERT into the home setting, investigator-led studies, advancing the overall management of patients and evaluating possible complementary therapies and to support the medical communication activities by reviewing and finalising core slide presentations on Hunter syndrome and its treatment, preparing review articles and providing advice and support for other media activities. The HOS European Expert Council meets twice a year.

expert advice and guidance on topics such as screening, diagnosis, ERT, management of patients

evaluating complementary therapies and support medical communication

3.3 Fabry Disease European Expert Council

expert advice and guidance

evolution of FD, diagnosis, ERT …

The role of the council is to provide expert advice and guidance in Europe on topics such as clinical aspects and disease evolution of Fabry Disease and disease diagnosis, enzyme replacement therapy for male and female patients, ERT for young oligo- or asymptomatic patients, moving ERT into the home setting, investigator-led studies, advancing the overall management of patients and evaluating possible complementary therapies and to support the medical communication activities. The Fabry European Expert Council meets twice a year.

3.4 Fabry Disease European Advisory Board

expert advice on clinical and scientific aspects related to FD

The role of the advisory board is to provide expert advice in Europe on all clinical and scientific aspects related to Fabry Disease. Particularly the FD board is concerned with the development of investigator-led studies to improve the knowledge on ERT with respect to dosing and treatment efficacy and the development of management guidelines and treatment recommendations. The Fabry European Advisory Board typically meets twice a year.

3.5 Gaucher Disease European Advisory Board

expert advice on clinical and scientific aspects related to GD

The role of the advisory board is to provide expert advice in Europe on all clinical and scientific aspects related to GD with particular emphasis on the development of consensus management and treatment guidelines. The GD European Advisory Board typically meets twice a year.

3.6 Pompe Disease European Advisory Board

expert advice on clinical and scientific aspects related to PD

The role of the advisory board is to provide expert advice in Europe on all clinical and scientific aspects related to PD and the communication to the medical community including management of clinical symptoms and complications, development of severity scores, recommendations for therapy and the use of diagnostic tools. The PD European Advisory Board typically meets twice a year.

Table 5: Seletected treatment centers for LSD in the European Community

EU medical centers		
Gaucher Disease	**Fabry Disease**	**Pompe Disease**
Mainz, Germany	Mainz, Germany	Mainz, Germany
Cologne, Germany	Copenhagen, Denmark	Munich, Germany
Cambrige, UK	Graches, France	Paris, France
London, UK	Lyon, France	Rotterdam, Netherlands
Manchester, UK	Prague, CZ	Vienna, Austria
Vienna, Austria	London, UK	London, UK
Warsaw, Poland	Amsterdam, Netherlands	Manchester, UK
Milano, Italy	Stockholm, Sweden	
Prague, CZ	Porto, Portugal	
Amsterdam, NL	Madrid, Spain	
Madrid, Spain	Kiel, Germany	
	Warsaw, Poland	
	Würzburg, Germany	
	Manchester, UK	
	Vienna, Austria	
MPS I	**MPS II**	**MPS VI**
Mainz, Germany	Mainz, Germany	Mainz, Germany
Warsaw, Poland	Manchester, UK	Manchester, UK
Padova, Italy	London, UK	London, UK
Zaragosa, Spain	Vienna, Austria	Graz, Austria
Prague, CZ	Salzburg, Austria	Padua, Italy
Manchester, UK	Padua, Italy	
Amsterdam, NL		
Vienna, Austria		
Dublin, Ireland		
Porto, Portugal		
Lyon, France		
Rotterdam, Netherlands		

4 Potential areas of conflict

4.1 Treatment costs and reimbursement issues

ERT is very expensive

limited attractiveness for pharmaceutical companies

"orphan drug status"

Enzyme replacement therapy for LSD is expensive (table 4) compared to treatment modalities for other rare inborn errors of metabolism (dietary therapy, co-factor substitution.). It is recognised that the development of drugs and the initiation of phase I-III trials to evaluate safety and efficacy for the treatment of a limited number of patients is very costly and therefore not very attractive for many pharmaceutical companies. On the other hand "orphan drug status" is granted for any newly developed drug that is licensed for the treatment for rare disorders (orphan diseases). This status permits extended exclusive licensure and return of profit for up to 15 years following initial approval by FDA or EMEA respectively. It is not known what percentage of the whole sale price (table 4) for each product is return of profit.

reimbursement conditions depend on the insurance systems

metabolic centers: Salzburg, Wien, Graz

Reimbursement by medical insurance companies and/or public health organisations may differ from country to country. In Austria reimbursement also varies depending in which federal state the affected individual lives or which health insurance company is involved. Following the approval of Elaprase® for the treatment of MPS II the oversight committee for health insurance companies ("Hauptverband der Sozialversicherungsträger") provided direct reimbursement of drug only if the therapy was given in one of three recognised metabolic centers (Salzburg, Wien, Graz). Enzyme replacement therapy for other LSD including Fabry Disease, Pompe Disease and MPS I are given at different levels (at the physician's office, at the peripheral hospital, at the metabolic center).

Table 6: estimated treatment costs per kg body weight per year in Austria (FAP-whole sale price (€); KKP*-insurance reimbursement (€)*

Prices LSD Austria							**calculations per infusion**					
	packing unit			**FAP***	**KKP***	**dosage**	**50 kg**	**n of vi-als**	**60 kg**	**n of vials**	**70 kg**	**n of vials**
Cerezyme	**200 U**	vial	1x	**929.15**	**870.55**							
Cerezyme	**400 U**	vial	1x	**1,833.65**	**1,741.10**	**60 U/ kg**	3.000 U	7	3.600 U	9	4.200 U	10
Fabrazyme	**5 mg**	vial	1x	**607.55**	**561.00**	**1 mg/ kg**	50 mg	10	60 mg	12	70 mg	14
Fabrazyme	**35 mg**	vial	1x	**3,915.70**	**3,745.00**							
Myozyme	**50 mg**	vial	10x	**5,746.20**	**5,500.00**	**20 mg/ kg**	1000 mg	20	1200 mg	24	1400 mg	28
Myozyme	**50 mg**	vial	25x	**14,317.95**	**13,750.00**							
Aldurazyme	**5.8 mg**	vial	1x	**831.75**	**770.00**	**0.5 mg/ kg**	25 mg	5	30 mg	5	35 mg	6
Elprase	**6 mg**	vial	1x	**1,249.76**	?	**0.5 mg/kg**	25 mg	4	30 mg	5	35 mg	6
Naglazyme	**5 mg**	vial	1x	**2,889.95**	?	**1.0 mg/kg**	50 mg	10	60	12	70	14
Replagal	**3.5 mg**	vial	1x	**4,052.57**	?	**0.2/kg**	10	3	12	4	14	4

4.2 Treatment guidelines –whom to treat, when to treat and when to discontinue treatment

limited number of published guidelines

There are only a limited number of published guidelines or recommendations for treatment and/or management of patients with LSD with the exception of GD [www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4118402 (Wraith et al. 2005. www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_073341 Vellodi et al.2007; Guigliani et al. 2007; Desnick et al. 2003; Eng et al. 2006; Ortiz et al. 2008; Pastores et al. 2004]

ERT developed and initiated over the last years…

… experience is still limited

Most of the enzyme replacement therapies have been developed and initiated over the last few years so that the cumulative experience is still limited. There is currently no consensus nor any data to support a consensus when to start ERT in male pediatric Fabry patients. Some colleagues decide to wait with ERT until the patient develops first symptoms (acroparesthesia, diarrhea..). Other colleagues argue that storage of Gl-3 is progressive and may damage kidneys irreversibly prior to the onset of clinical symptoms and initiation of ERT.

no consensus when to start ERT

no recommendations when to discontinue ERT

In contrast there are no recommendations when to discontinue ERT in patients with LSD, although discontinuation should be considered in any patient who is non-compliant or where ERT clearly has not proven to be effective. The latter may only be evaluated if therapeutic goals have been formulated at the onset of ERT and are checked at regular intervals to ensure continued compliance and efficacy of treatment.

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Medical information (academic institutions and patient support groups)

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Medical information (disease specific)

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Pharmaceutical industry (related to enzyme replacement therapy)

1. www.actelion.com (manufacturer of substrate reduction therapy for the therapy of Gaucher disease)
2. www.amicustherapeutics.com (pharmaceutical company that investigates novel forms of therapy for LSD)
3. www.biomarinpharm.com (manufacturer of recombinant enzyme for the therapy of MPS-VI)
4. www.genzyme.com (manufacturer of recombinant enzyme for the therapy of Fabry disease, Gaucher disease, Pompe disease, MPS-I). Additional *Genzyme* websites include www.aldurazyme.com, www.pompe.com
5. www.shire.com (manufacturer of recombinant enzyme for the therapy of Fabry disease, Gaucher disease, MPS-II)