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Enzyme Replacement Therapy for Lysosomal Storage Diseases

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

This EPC evidence report is a Technical Brief. A Technical Brief is a rapid report, typically on an emerging medical technology, strategy or intervention. It provides an overview of key issues related to the intervention -- for example, current indications, relevant patient populations and subgroups of interest, outcomes measured, and contextual factors that may affect decisions regarding the intervention. Although Technical Briefs generally focus on interventions for which there are limited published data and too few completed protocol-driven studies to support definitive conclusions, the decision to request a Technical Brief is not solely based on the availability of clinical studies. The goals of the Technical Brief are to provide an early objective description of the state of the science, a potential framework for assessing the applications and implications of the intervention, a summary of ongoing research, and information on future research needs. In particular, through the Technical Brief, AHRQ hopes to gain insight on the appropriate conceptual framework and critical issues that will inform future comparative effectiveness research.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this Technical Brief. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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Enzyme Replacement Therapy for Lysosomal Storage Diseases

Structured Abstract

Background. Lysosomal storage disorders (LSD) comprise about 50 incurable monogenetic autosomal or sex-linked diseases with an estimated combined incidence of 1 in 1,500 to 7,000 births. They occur secondary to genetic mutations that result in the deficiency of native intracellular enzymes that catabolize biological macromolecules. These enzyme deficiencies result in accumulation of specific macromolecular storage compounds within lysosomes in various tissues and organs, causing progressive damage. LSD management traditionally involved supportive care measures tailored to disease stage, the organs and systems involved, and the degree of impairment. However, enzyme-replacement therapy (ERT) is now commercially available for six LSDs, typically used lifelong with traditional management practices for each.

Purpose. The objective of this Technical Brief is to provide an overview of the current state of FDA-approved ERT for the treatment of six LSDs. The document also addresses key unresolved or controversial issues surrounding the use of ERT to treat LSDs.

Methods. Four Guiding Questions were used to frame this Brief. An environmental scan of the literature from 1990 through mid-September 2011 included primary studies, as well as narrative and systematic review articles to create an overview of reported clinical outcomes. Other information sources included dosing and other treatment-related information from the U.S. Food and Drug Administration (FDA) -approved product labels; scientific information packages from the product manufacturers that included unpublished data; and, interviews with physician Key Informants and patient advocates.

Findings. Published clinical studies report a variety of benefits associated with FDA-approved ERT. Followup in clinical studies was as short as 10 weeks to as long as 4 to 5 years. Intermediate and clinical outcomes varied. Some were disease-specific intermediate outcomes, such as plasma levels of storage compounds. Others were common hematological measures (e.g., anemia, thrombocytopenia), bone pain and skeletal abnormalities, renal function, cardiac function, pulmonary function, growth, and the 6-minute walk test. Plasma levels of storage compounds were linked with subsequent clinical outcomes, for example, renal, cardiac, or cerebrovascular, in some diseases. Harms reported to the FDA and in clinical studies were primarily allergic, including infusion-associated reactions and anaphylaxis at rechallenge, and immunogenic, primarily an IgG-type antibody response. Clinical studies did not detect adverse events attributed to a specific pharmacodynamic effect of the glycoprotein ERT products; the Key Informants also reported no agent-specific adverse events in their patients, regardless of the LSD and ERT used to treat it. Our review of selected clinical studies, narrative reviews, Key Informant discussions, patient advocate interviews, and publicly available information from grey literature sources suggest a number of issues remain to be solved, including dose optimization, optimal timing of ERT, and pharmacokinetic and pharmacodynamic optimization of ERT products.

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Background

Lysosomal Storage Diseases

Lysosomes are generally spherical, subcellular organelles bounded by a single layer membrane within eukaryotic cells. They are ubiquitous structures which contain an array of glycoprotein acid hydrolase enzymes, all of which are synthesized in the endoplasmic reticulum and modified in the Golgi apparatus. These enzymes catabolize all major classes of biological macromolecules such as proteins, nucleic acids, glycosphingolipids, mucopolysaccharides, and glycogen, as well as sequestered bacteria, viruses, and other foreign substances that are taken up by phagocytosis into white blood cells and macrophages. Lysosomes are also responsible for autophagy, the gradual turnover of each cell's own components as they age and become obsolescent. They may be considered the main site of intracellular digestion and housekeeping.

Lysosomal storage disorders (LSD) comprise a group of monogenetic autosomal or sex-linked diseases that occur secondary to genetic defects (e.g., single nucleotide substitutions, frameshift mutations, gene deletions) that reduce the activity, or cause total deficiency, of the native enzymes within the lysosomes.[1-3] This allows macromolecular storage compounds that are normally catabolized to accumulate within these organelles, expanding them and causing progressive damage in connective tissue, skeletal structure, various organs, and, in some cases, the central nervous system, leading to physical deterioration, impairment, and, potentially, death.

LSDs are broadly divided into groups based on the nature of the stored substrate: mucopolysaccharidoses (MPS), lipidoses, glycogenoses, and oligosaccharidoses. They are rare diseases, with an estimated combined incidence of 1 in 1,500 to 7,000 live births. Some 50 different LSDs have been identified.[3] Six of these disorders have commercially available therapeutic products available to treat them, known as enzyme replacement therapy (ERT). These LSDs may exhibit infantile, juvenile, and adult forms. In adult-onset diseases, the pathogenesis is usually slower than in the infantile or juvenile forms, and are characterized mainly by peripheral symptoms. By contrast, infantile and juvenile forms often involve progressive central nervous system involvement in addition to peripheral symptoms.

Each LSD also often exhibits significant heterogeneity in its ultimate expression, with early or late presentation of symptomatic pathology that may be a function of mutation type and residual enzyme levels.[4] Although specific mutations or types of mutations may be connected to discrete disease effects, genotype-phenotype correlations are generally not strong, which may complicate clinical decision making in terms of appropriate therapeutic approach.[4]

Therapeutic Measures for Lysosomal Storage Diseases

As outlined for each LSD in Table 1, supportive care measures are used to manage patients with pathology that develops within the organs and systems involved, according to the degree of physical impairment.[1-3, 5, 6] For example, patients with Gaucher disease type I, the most common LSD, may develop visceral problems (e.g., hepatomegaly, splenomegaly), anemia, thrombocytopenia, lung disease, severe bone pain (acute or chronic), avascular necrosis, and have growth impairment and pubertal delay.[7] Supportive care may then consist of a combination of therapies that include blood transfusion, bed rest, analgesia, anti-inflammatory agents, hyperbaric oxygen, and surgery (splenectomy, orthopedic procedures). In any LSD, once pathology develops, it may become irreversible despite the use of ERT and supportive care.

Table 1. Lysosomal storage diseases with U.S. Food and Drug Administration (FDA) -approved enzyme replacement therapy

Disease	Estimated Incidence	Deficient Enzyme	Pathological Lysosomal Storage Product	Clinical Description and Expression
Fabry Disease	1/40,000 live male births	α-galactosidase A	glycosphingolipids, predominantly globotriaosylceramide and galabiosylceramide	Fabry disease is an X-linked disorder with an onset of symptoms and severity of symptoms that vary widely among patients. Males may exhibit symptoms in childhood or adolescence, or remain asymptomatic into adulthood. Female carriers may be asymptomatic or have symptoms as severe as affected males. Early symptoms include corneal and lenticular opacities, skin lesions, pain in the extremities, decreased ability to sweat, gastrointestinal symptoms such as chronic abdominal pain and diarrhea, followed by slow decline in kidney function. Fabry pain crises consist of burning, tingling, numbness in the hands and feet, which can last several hours to days. Life expectancy is 40 - 50 years, with cause of death usually due to a decline in kidney function or to cardiovascular disease.
Gaucher type I	Overall 1/50,000 live births 1/500-1000 live births among Ashkenazi Jewish population	glucocerebrosidase	glucosylceramide	Gaucher disease type I is the most common lysosomal storage disease. The onset of symptoms is variable, from early childhood to late adulthood. Patients presenting in early childhood have a more severe course of the disease compared to those presenting later in life. Symptoms include anemia, hepatosplenomegaly, skeletal disorders and lung and kidney impairment. The clinical course, disease progression, and severity among the different organ systems vary markedly among cases. There can be both central and peripheral nervous system involvement in this form of the disease, but there is no neuronal loss. Some developmental delays may occur as a consequence of the persistent clinical symptoms. Life expectancy varies widely, depending on the severity of symptoms, and can extend to near normal expectancy.

Table 1. Lysosomal storage diseases with U.S. Food and Drug Administration (FDA) -approved enzyme replacement therapy (continued)

Disease	Estimated Incidence	Deficient Enzyme	Pathological Lysosomal Storage Product	Clinical Description and Expression
Glycogen Storage Disease type II (Pompe disease)	1/40,000 live births	acid alpha-glucosidase	glycogen	There are two forms of Pompe disease. Symptoms appear in the first few months of life in the infantile form of the disease. There are feeding problems, poor weight gain, muscle weakness, floppiness, head lag, respiratory difficulties, and an enlarged heart. Life expectancy is <1 year, with cause of death usually from cardiorespiratory failure or respiratory infection. Onset of symptoms in the juvenile/adult form of the disease ranges from the 1st decade to the 6th decade of life. Severity of symptoms varies markedly among patients. Patients experience muscle weakness, progressive respiratory weakness, and either no or mild cardiac insufficiencies. Life expectancy is variable, depending on severity and rate of disease progression, with cause of death usually due to respiratory failure.
MPS I (Hurler disease)	1/100,000 live births	alpha-L-iduronidase	glycosaminoglycans dermatan sulfate and heparan sulfate	MPS I is a variable disorder with a wide range of symptoms that differ among patients in which symptoms develop, age at onset and severity. Though the symptoms manifest in a continuous spectrum among patients, for clinical purposes, they are categorized into the following three groups: MPS IH, Hurler, is the most severe form with symptoms presenting within the first 12 months of age. Symptoms may include respiratory insufficiency, hearing loss, joint movement restriction, enlargement of the heart, spleen, and liver, and progressive mental retardation. Life expectancy is < 10 years, with cause of death most commonly due to obstructive airway disease, upper respiratory infections, or cardiac complications. MPS IH/S, Hurler/Scheie, is an intermediate form of the disease with symptoms presenting usually from 3-6 years of age. Symptoms may include growth deficiencies, deafness, coarse facial features, clouded corneas, umbilical hernia, heart disease, and moderate mental retardation. Life expectancy for Hurler/Scheie is late teens to early twenties. MPS IS, Scheie, is the mildest form of the disease with symptoms presenting from 5-12 years of age. Symptoms may include stiff joints, clouded corneas, aortic regurgitation, normal intelligence or mild learning disabilities and psychiatric problems. Life expectancy extends into adulthood, though there is significant morbidity.

Table 1. Lysosomal storage diseases with U.S. Food and Drug Administration (FDA) -approved enzyme replacement therapy (continued)

Disease	Estimated Incidence	Deficient Enzyme	Pathological Lysosomal Storage Product	Clinical Description and Expression
MPS II (Hunter disease)	Overall 1/155,000 live births 1/34,000 live births in Jewish population in Israel	iduronate sulfatase	glycosaminoglycans dermatan sulfate and heparan sulfate	MPS II is an X-linked disorder. The clinical symptoms of MPS II are highly variable, differing among patients in which symptoms develop, age of onset and severity. For clinical purposes, MPS II is divided into two forms, a severe form and an attenuated form. The more severe form has CNS involvement with symptoms presenting by 2 years of age. Symptoms may include short stature, organomegaly, joint stiffness, hearing loss, progressive cognitive deterioration, progressive airway disease, and cardiac disease. Life expectancy ranges from 10-20 years, with cause of death usually due to heart disease, from valvular, myocardial, and ischemic factors. Patients with the milder form of the disease may not be diagnosed until school-age, adolescence, or adulthood. The physical symptoms may include the same as the severe form, but are milder in nature. There is usually no CNS involvement. Life expectancy is 20-60 years.

Table 1. Lysosomal storage diseases with U.S. Food and Drug Administration (FDA) -approved enzyme replacement therapy (continued)

Disease	Estimated Incidence	Deficient Enzyme	Pathological Lysosomal Storage Product	Clinical Description and Expression
MPS VI (Maroteaux- Lamy syndrome)	1/340,000 live births	arylsulfatase B	dermatan sulfate	As with the other forms of MPS, the following vary among patients: which symptoms develop, age of onset of symptoms, and severity of symptoms. An enlarged head and deformed chest may be present at birth. Growth and development can be normal the first few years of life, but appear to stop around age 6. The clinical characteristics are similar to MPS I, except with a later onset and a slower progression of symptoms. Mental development is usually normal, but psychomotor skills are affected by the physical and visual impairments of the disease. Life expectancy depends on severity of symptoms, ranging from <20 years to later adulthood, with cause of death usually from heart disease or airway obstruction.

*Textbook Sources:

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Enzyme Replacement Therapy

ERT products are exogenously administered glycoproteins, intended to replace specific endogenous defective, less active, or totally absent, enzymes in patients with one of six LSDs.[2, 3, 6, 8-14] They are administered by intravenous infusion, at dosages typically based on patient body weight, usually weekly or every other week, for the life of a patient. The infused enzymes are taken up by cells and transported into lysosomes, where they catabolize the specific substrate that has accumulated.

Among six commercially available ERT products, five are produced using recombinant DNA methods in cell cultures. The sixth, alglucerase (Ceredase®), is prepared from a large pool of human placentae collected from selected donors. Compared to the recombinant DNA-produced products, the source of alglucerase has two practical implications that potentially limit its use. The first limitation is the large number of placentae required to produce this product, approximately 10 to 12 tons, or about 50,000 annually per patient.[15] A second potential limitation is the risk for transmission of viral diseases. Steps have been introduced into the manufacturing process of alglucerase to reduce the risk of viral contamination. Each lot of alglucerase is tested for hepatitis B surface antigen (HBsAg) and for human immunodeficiency virus antigen (HIV-1) and antibody (HIV-1/2). While no procedure has been shown to be totally effective in removing viral infectivity, viral disease transmission with alglucerase has not been reported in the literature.

ERT can pose issues related to resources, as use is lifelong (perhaps decades) with an average annual drug cost of $300,000 for a 30- to 40-kg individual in the U.S.[1, 16] This amount does not account for additional costs from hospitals, private offices, or infusion centers, nor does it reflect the cost of supplies, infusion charges, or other necessary medications and therapies.[17] In the U.S., FDA-labeled uses for ERT are covered by third-party payers, but maximum lifetime insurance limits may be reached within 2 to 5 years after starting treatment.[17] Some cost may be reduced with home infusion,[18-25] but cost for these products is still very high for most families.

Substrate Reduction Therapy

Substrate reduction therapy (SRT) has been proposed as another strategy to treat LSDs.[26-35] SRT refers to the inhibition of synthesis of lysosomal storage macromolecules that accumulate in the tissues and organs of patients with LSDs. It is, therefore, the opposite of ERT, which works by providing exogenous enzymes to break down lysosomal storage macromolecules. Furthermore, the effectiveness of SRT depends on the existence of residual catabolic enzyme activity specific to the storage substance and disease for which it is used. Thus, if the rate of synthesis of a storage product is reduced, residual enzyme levels may be sufficient to degrade it, thereby reducing accumulation.

One SRT product—miglustat—has received FDA marketing approval for treatment of type I Gaucher disease.[30, 33] Miglustat (N-butyl-deoxynojirimycin, NB-DNJ) is an orally active member of the iminosugar class of small molecules, polyhydroxylated alkaloids that are structural mimics of monosaccharides and inhibit the activity of ceramide glucosyltransferase. This enzyme catalyzes the first committed step of glycosphingolipid synthesis, thereby reducing the rate of formation of glucosylceramide, the storage compound involved in the pathogenesis of Gaucher disease.[34] Unlike ERT products, miglustat can cross the blood-brain barrier, and thus is theoretically capable of treating CNS manifestations and symptoms of Gaucher disease.

Miglustat (Zavesca®, Actelion Pharmaceuticals) received FDA marketing approval in August 2003 for adult patients only with mild-to-moderate type 1 Gaucher disease for whom ERT is not a therapeutic option (e.g., due to constraints such as allergy, hypersensitivity, or poor venous access) (http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021348s008lbl.pdf). This agent is not an ERT product and will not be considered in detail in this Brief.

Technical Brief Objective

The objective of this Technical Brief is to provide an overview of the current state of FDA-approved ERT for the treatment of six lysosomal storage disorders shown in Table 1. Substrate reduction therapy with miglustat will not be considered further in this Brief, as it is by definition not ERT. Four Guiding Questions (following) address the clinical indications for each ERT, potential benefits and harms associated with each ERT product, and dosing and administration details of each ERT. An environmental scan of the literature provides a picture of published evidence on clinical use of these agents for each LSD. This Brief also discusses key unresolved or controversial issues surrounding the use of ERT to treat lysosomal storage diseases, based on the literature and information obtained through semi-structured, one-on-one telephone interviews with Key Informants.

Guiding Questions

1. What FDA-approved enzyme replacement therapy (ERT) products are available for lysosomal storage diseases (LSD)?
   a. What are the clinical indications for each FDA-approved ERT product?
   b. What are the theoretical benefits of ERT for LSDs?
   c. What are the potential safety issues and harms with ERT?

2. What is the context in which each FDA-approved ERT product is used?
   a. What are the FDA-approved dose regimens for each ERT product?
   b. Where and by whom is ERT administered?
   c. What adjunct treatments are used with each FDA-approved ERT product?

3. What published and unpublished studies have reported on the use and safety of this intervention?
   a. Type of ERT
   b. Indication/patient inclusion criteria
   c. Study design/size
   d. Comparator used in comparative studies
   e. Concurrent/prior treatments
   f. Length of followup
   g. Outcomes measured

4. What are key unresolved or controversial issues with ERT in LSDs?

Methods

Several sources were used to inform this technical brief. Information was collected in a review of published medical literature, narrative review articles, a search of the grey literature, and discussions with Key Informants.

Guiding Questions 1 and 2 relied on information from published narrative reviews and information in the grey literature. The latter may include information culled from websites of pharmaceutical companies, patient advocacy groups, and other sources such as the FDA-approved prescribing information for each ERT product.

Guiding Question 3 was addressed through an environmental scan of the literature, including primary and secondary (narrative and systematic reviews) articles. Key Informants provided guidance on the potential clinical outcomes of interest and the potential benefits and harms of ERT as the review was conducted.

Guiding Question 4 relied on integrating information from Key Informants, grey literature, published primary studies and narrative reviews.

Data Sources

Discussions with Key Informants

The Key Informants included content experts and a payer representative from the Medicaid Medical Directors Learning Network. The content experts primarily included specialists in metabolic diseases, lysosomal storage diseases, and rare diseases.

Two Key Informant group conference calls were conducted. The Key Informants provided input on the literature review, for example, years to include in the search and potential clinical outcomes. As a followup to the group conference calls, the Key Informants were interviewed individually by telephone, using a semi-structured interview outline that provided opportunity to share their clinical experiences with patients with lysosomal storage disorders, their experience with ERT, and their opinions on unresolved or controversial issues relating to ERT. The seven questions we asked in the interviews follow:

1. Have you seen patients in your practice with any of the six diseases covered in this report (MPS I, MPS II, MPS VI, Gaucher, Fabry, Pompe)?
2. What challenges, successes, and failures have you experienced in treating these patients?
3. What factors do you consider before starting ERT with your patients?
4. What outcomes, beneficial and harmful, have you seen in your patients treated with ERT?
5. What do you believe are unresolved issues surrounding ERT?
6. In your view, what needs to be done to resolve these issues, for example by pharmaceutical companies, researchers, or practitioners?
7. Are you aware of any new ERT products or developments in the development or testing phase that are not common knowledge?

Discussions with Patient Advocates

One call with the patient advocates was conducted. Because of the nature of LSDs, patients are predominantly children, so one adult patient and one parent of a child patient were consulted. The adult patient and the parent were asked about their experiences with the disorder prior to

ERT and subsequent to ERT. They were asked to describe symptoms, clinical outcomes of importance to them, and factors involved in the decision to begin treatment with ERT.

Grey Literature Search

The U.S. Food and Drug Administration (FDA) website concerning the six ERT treatments was accessed. Information was gathered to inform Guiding Questions 1 and 2.

ERT manufacturers provided scientific information packages (SIPs) that contained product information, unpublished data, and a bibliography. Their websites were accessed to inform Guiding Questions 1 and 2, using the following Web links:

Biomarin Pharmaceuticals
http://www.bmrn.com/products/naglazyme.php
http://www.bmrn.com/products/aldurazyme.php

Genzyme Corporation
http://www.aldurazyme.com/global/az_us_home.asp
http://www.fabrazyme.com/global/fz_us_hp_homepage.asp
http://www.cerezyme.com/
http://www.myozyme.com/

Shire Human Genetic Therapies, Inc.
www.vpriv.com
www.elaprase.com

Registries and patient advocate websites for each of the six LSDs were accessed. Examples included:

http://www.marrow.org/PATIENT/Undrstnd_Disease_Treat/Lrn_about_Disease/Metabolic_Storage/Hurler_and_Treatment/index.html
http://www.mpssociety.co.uk/index.php?page=hunter-disease
http://www.mpssociety.org.au/MPS%20Diseases/mpsviregistry.htm
https://www.registrynxt.com/Gaucher/Pages/RegistryNXTHome.aspx
https://www.lsdregistry.net/fabryregistry/
http://www.pompe.com/en/healthcare-professionals/pompe-registry.aspx

Current clinical trials involving ERT were identified by searching http://clinicaltrials.gov/ct.

Published Literature Search

We did not perform a systematic review of the literature. Instead, an environmental scan of published medical literature was performed via electronic searches of MEDLINE®, EMBASE®, the Cochrane Database, and the Health Technology Assessment Database to address Guiding Question 3. Based on input from the Key Informants, the searches encompassed the years 1990 through September 16, 2011, as outlined in Appendix A. Initiation in 1991 corresponds to the year the first ERT product (alglucerase) received FDA marketing approval.

The DistillerSR® Systematic Review Tool was utilized to facilitate the screening and study selection process. Titles and abstracts were examined using Distiller® to identify articles for

potential inclusion. We initially retrieved selected narrative or systematic review articles on ERT for the pertinent LSDs to provide background material. Preclinical studies, foreign-language articles, editorials, comments, and letters to the editor were excluded in the title and abstract screen. Studies were eligible for full-text screening if the abstract reported clinical outcomes in patients who received ERT to treat an LSD.

Full-text articles were retrieved and screened for inclusion/exclusion in the literature scan. Primary study selection criteria included well-described prospective clinical studies, randomized trials, and other comparative studies that reported health outcomes in patients with one of the six LSDs under consideration who received ERT for that disorder. We also sought large, representative registry reports to ascertain clinical outcomes reported in that type of publication. Reference lists of the included studies and recent review articles were scrutinized to identify other relevant articles. Study quality was not assessed in this Brief.

Data Organization and Presentation

Information Management

Three main sources of information were consulted for this technical brief: published literature, grey literature, and Key Informants. Data from studies published in the medical literature were abstracted into Microsoft Word® tables. Data collected include: study design, number of study subjects, subject age, severity of disease, ERT dosing and administration details, length of followup, and clinical outcomes.

Information about clinical indications, ERT dosing, and administration, abstracted from review articles and from the FDA-approved prescribing information for each ERT product, was organized in tables. Information from Key Informants and patient advocates was managed in a Word document.

Data Presentation

Summary tables present selected published studies for each disease, and include the following information: study design, patient population, interventions, dose regimen, followup duration, and clinical outcomes that were measured. A narrative summary integrated information gathered from the medical literature, FDA-approved documentation, the grey literature, and the Key Informants, to describe the current state of ERT treatment, clinical indications, dosing and administration details, and a discussion of the key unresolved or controversial issues regarding the treatment.

Findings

Guiding Question 1: What FDA-approved enzyme-replacement therapy (ERT) products are available for lysosomal storage diseases (LSD)?

Table 2 lists ERT products that are commercially available in the U.S. and their marketing approval dates. All products were approved under stipulations of the FDA Orphan Drug Act (ODA) of 1983, which provides for granting special status to a product to treat a rare disease or condition upon request of a sponsor (**http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/OrphanDrugAct/default.htm**).

According to the ODA, a product intended to treat a rare disease or condition must meet certain criteria, particularly that the disease or condition for which the drug is intended affects fewer than 200,000 people in the U.S. or, if the drug is a vaccine, diagnostic drug, or preventive drug, the persons to whom the drug will be administered in the U.S. are fewer than 200,000 per year. This status is referred to as orphan designation. The approval of an orphan designation request does not alter the standard regulatory requirements and process for obtaining marketing approval. The safety and efficacy of a compound must be established through adequate and well-controlled studies.

Due to the massive financial investment required to produce orphan drugs, prior to the passage of the ODA, very few companies invested in the development of these drugs. Additionally, because the target population for orphan drugs is extremely small, the long-term return on investment for these drugs is extremely low. The ODA provides pharmaceutical companies who develop orphan drugs with a tax credit to help offset the cost to conduct clinical trials. The act also grants a 7-year period of market exclusivity to prevent other companies from developing and competing with similar products.

What are the clinical indications for each FDA-approved ERT product?

Table 2 lists the FDA-approved ERT products, the clinical indications for each, and the outcomes that were measured, according to the FDA-approved prescribing information. There is no off-label use for these agents, with the exception of dose regimen variations, for example in patients with type I Gaucher disease.[36-38]

The indications shown in Table 2 are specific to the disease in question and are based on data from clinical trials, some of which are shown in summary tables under Guiding Question 3 of this Brief. For example, in three published clinical studies of agalsidase beta for Fabry disease (reviewed later), a key endpoint was reduction of globotriaosylceramide (GL-3) inclusions in the capillary endothelium of the kidney, heart, and skin, measured by light microscopy in biopsy specimens.[39-41] In a randomized, placebo-controlled trial, accumulation of GL-3 in these cells was considered to be a surrogate marker for the subsequent development of renal, cardiac, and cerebrovascular disease, which lead to high morbidity and premature mortality.[40] A subsequent post-approval randomized, double-blind placebo-controlled trial was required by FDA to demonstrate clinical benefit, reflected by correlation of inclusion clearance and subsequent composite clinical outcomes related to renal, cardiac and cerebrovascular disease.[39]

Table 2. FDA-approved prescribing information for enzyme replacement therapy products for lysosomal storage diseases

Disease	Product	Manufacturer	FDA Approval Date	Clinical Indication and Outcomes Measured in the FDA-Approved Prescribing Information (source)
Fabry Disease	Fabrazyme® (agalsidase beta)	Genzyme Corporation	April 2003	Agalsidase beta is indicated for use in patients with Fabry disease. It reduces globotriaosylceramide (GL-3) deposition in capillary endothelium of the kidney and certain other cell types. (http://www.fabrazyme.com/hcp/pi/fz_us_hc_pi.pdf)
Gaucher Disease type I	Ceredase® (alglucerase)	Genzyme Corporation	April 1991	Alglucerase for injection is indicated for use as a long-term enzyme replacement therapy for children, adolescents and adult patients with a confirmed diagnosis of type I Gaucher disease who exhibit signs and symptoms that are severe enough to result in one or more of the following conditions: • moderate-to-severe anemia • thrombocytopenia with bleeding tendency • bone disease significant hepatomegaly or splenomegaly http://ww(w.accessdata.fda.gov/drugsatfda_docs/label/2006/020057s034lbl.pdf)
	Cerezyme® (imiglucerase)	Genzyme Corporation	May 1994	Imiglucerase for injection is indicated for long-term enzyme replacement therapy for pediatric and adult patients with a confirmed diagnosis of type 1 Gaucher disease that results in one or more of the following conditions: • anemia • thrombocytopenia • bone disease • hepatomegaly or splenomegaly (http://www.cerezyme.com/~/media/Files/CerezymeUS/pdf/cerezyme_pi.pdf)
	Velaglucerase® (velaglucerase alfa)	Shire Human Genetic Therapies Inc.	March 2010	Velaglucerase alfa for injection is a hydrolytic lysosomal glucocerebroside-specific enzyme indicated for long-term enzyme replacement therapy (ERT) for pediatric and adult patients with type 1 Gaucher disease. (http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022575lbl.pdf)
Glycogen Storage Disease type II (Pompe disease)	Myozyme® (alglucosidase alfa)	Genzyme Corporation	April 2006 for infantile onset form only	Alglucosidase alfa is indicated for use in patients with Pompe disease (GAA deficiency). It has been shown to improve ventilator-free survival in patients with infantile-onset Pompe disease as compared to an untreated historical control, whereas use in patients with other forms of Pompe disease has not been adequately studied to assure safety and efficacy. (http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/125141_74lbl.pdf)

Table 2. FDA-approved prescribing information for enzyme replacement therapy products for lysosomal storage diseases (continued)

Disease	Product	Manufacturer	FDA Approval Date	FDA-Approved Labeled Indication (source)
MPS I (Hurler disease)	Aldurazyme® (laronidase)	Genzyme Corporation	April 2003	Laronidase is a hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme indicated for patients with Hurler and Hurler-Scheie forms of mucopolysaccharidosis I and for patients with the Scheie form who have moderate to severe symptoms. The risks and benefits of treating mildly affected patients with the Scheie form have not been established. Laronidase has been shown to improve pulmonary function and walking capacity. It has not been evaluated for effects on the central nervous system manifestations of the disorder. (http://www.aldurazyme.com/pdf/az_us_hc_pi.pdf)
MPS II (Hunter disease)	Elaprase® (idursulfase)	Shire Human Genetic Therapies Inc.	July 2006	Idursulfase is indicated for patients with Hunter syndrome (mucopolysaccharidosis II). It has been shown to improve walking capacity in these patients. (http://www.elaprase.com/pdf/Elaprase_V5.pdf)
MPS VI (Maroteaux-Lamy syndrome)	Naglazyme® (galsulfase)	BioMarin Pharmaceutical Inc.	June 2005	Galsulfase is a hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme indicated for patients with mucopolysaccharidosis VI (Maroteaux-Lamy syndrome). It has been shown to improve walking and stair-climbing capacity. (http://www.naglazyme.com/en/documents/Naglazyme_Prescribing_Information.pdf)

The first ERT product for type I Gaucher disease (alglucerase) received approval based on effects on surrogate markers, including hemoglobin levels and platelet counts; splenic and hepatic volumes measured by computed tomography (CT) or magnetic resonance imaging (MRI); and skeletal involvement reflected by serum acid phosphatase activity.[42] As shown later in this Brief, subsequent studies for the more recently approved products for type I Gaucher disease (imiglucerase, velaglucerase) used similar disease surrogates, as well as clinical outcomes such as bone pain, bone crisis, pathologic fractures, mobility, and quality of life (SF-36 general health survey).[15, 43-46]

As shown in Table 2, and the summary tables for clinical studies of these diseases under Guiding Question 3, the other four commercially available ERT products received approval based on their effects on disease-specific clinical outcomes, including, but not limited to, walking (laronidase for MPS I, idursulfase for MPS II, galsulfase for MPS VI) or stair-climbing capacity (galsulfase) and pulmonary capacity and function (alglucosidase alfa for Pompe disease, laronidase for MPS I).

What are the theoretical benefits of ERT for LSDs?

Potential responses to ERT are outlined according to disease in Table 3, based on information obtained from the FDA-approved product labels and from narrative review articles.[1, 2, 6, 8-10, 13, 47, 48]

Table 3. Theoretical responses to ERT for lysosomal storage diseases

Disease	Outcome measure [1, 2, 6, 8-10, 13, 47, 48]
Fabry Disease	• Renal function • Vascular lesions • Myocardial function • Nerve fiber conduction • Neuropathic pain • Tolerance to cold and heat
Gaucher Disease type I	• Hepatic or splenic volume • Hematological measures • Bone manifestations
Glycogen Storage Disease type II (Pompe disease)	• Lifespan • Cardiac symptoms • Myocardial function • Skeletal muscle function • Walking ability
MPS I H-S and S (Hurler disease)	• Urinary glycosaminoglycan levels • Hepatic or splenic volume • Airway patency and sleep apnea • Myocardial function • Range of motion in joints • Growth rate
MPS II (Hunter disease)	• Urinary glycosaminoglycan levels • Hepatic and splenic volume • 6-minute walk test • Range of motion in joints
MPS VI (Maroteaux-Lamy syndrome)	• Urinary glycosaminoglycan levels • Range of motion in joints • Joint pain

According to interviews with Key Informant clinical experts, the effects of ERT may vary within each LSD for which it is indicated, related to the clinical manifestations and stage of

disease at the time ERT is initiated. Our Key Informants further suggested that the effect of timing ERT initiation on clinical parameters is not well understood.

What are the potential safety issues and harms with ERT?

The FDA-approved prescribing information for each ERT product indicates infusion-associated adverse events may occur in recipients. These include pyrexia, chills, hypertension, tachycardia, cutaneous reactions (rash, pruritis, erythema, urticaria), burning, swelling, headache, nausea, fatigue, malaise, joint pain, dyspnea, facial edema, dizziness, bronchospasm, and others (Table 4).

Table 4. Adverse effects of ERT reported in the FDA-approved label

Disease	Generic name	Infusion-related	IgG-positivity	IgE-Mediated (Black Box Warning)
Fabry Disease	Agalsidase alfa Agalsidase beta	•	•	
Gaucher Disease type I	Alglucerase Imiglucerase Velaglucerase	•	•	
Glycogen Storage Disease type II (Pompe disease)	Alglucosidase alfa	•	•	•
MPS I H-S and S (Hurler disease)	Laronidase	•	•	•
MPS II (Hunter disease)	Idursulfase	•	•	•
MPS VI (Maroteaux-Lamy syndrome)	Galsulfase	•	•	

The FDA-approved label for each ERT product also reports immunogenic effects, primarily elicitation of IgG-type antibodies, in varying proportions of study subjects (Table 4). The prescribing information for these products cautions that interpretation of immunogenicity results is affected by the sensitivity and specificity of the assay, and that the incidence of antibody positivity may be influenced by a number of factors related to assay methodology, sample handling, timing of sample collection relative to dosing, concomitant medications, and underlying disease. Whether elicited IgG antibodies have an effect on long-term efficacy of ERT products has not been determined.

Black box warnings appear on the FDA-approved label for three ERT products (alglucosidase alfa [Myozyme®]; idursulfase [Elaprase®]; laronidase [Aldurazyme®]), indicating life-threatening anaphylactic reactions have been observed in some patients during infusion (Table 4). The label for a fourth product, agalsidase beta (Fabrazyme®) indicates that life-threatening anaphylactic reactions and severe allergic reactions have been observed in some patients during infusions, but the information is not specifically included as a black box warning.

The prescribing information for each product reports adverse events were noted in a low proportion of ERT recipients, but none have been attributed to a specific action of the glycoprotein itself. This concurs with the clinical experience reported by the Key Informants for this Brief, who reported infusion-related reactions and immunogenic events in their patients; it also concurs with results reported in the clinical studies summarized under Guiding Question 3.

Guiding Question 2: What is the context in which each FDA-approved ERT product is used?

What are the FDA-approved dose regimens for each ERT product?

The dose regimen specified in the FDA-approved label for each ERT product is shown in Table 5. All ERT products are infused intravenously, typically over periods of 1 to 4 hours, as specified.

Table 5. FDA-approved label dose regimens for ERT products

Disease	Product	Dose Regimen (link)
Fabry Disease	Fabrazyme® (agalsidase beta)	1 mg/kg body weight infused intravenously every two weeks (http://www.fabrazyme.com/hcp/pi/fz_us_hc_pi.pdf)
Gaucher Disease type I	Ceredase® (alglucerase)	2.5 units/kg of body weight infused intravenously three times a week up to as much as 60 units/kg administered as frequently as once a week or as infrequently as every four weeks 60 units/kg infused intravenously every two weeks is the dose for which the most data are available (http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/020057s034lbl.pdf)
	Cerezyme® (imiglucerase)	2.5 units/kg of body weight infused intravenously three times a week up to as much as 60 units/kg administered as frequently as once a week or as infrequently as every four weeks 60 units/kg infused intravenously every two weeks is the dose for which the most data are available (http://www.cerezyme.com/~/media/Files/CerezymeUS/pdf/cerezyme_pi.pdf)
	Velaglucerase® (velaglucerase alfa)	60 units/kg body weight infused intravenously every two weeks (http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022575lbl.pdf)
Glycogen Storage Disease type II (Pompe disease)	Myozyme® (alglucosidase alfa)	20 mg/kg body weight infused intravenously every two weeks (http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/125141_74lbl.pdf)
MPS I H-S and S (Hurler disease)	Aldurazyme® (laronidase)	0.58 mg/kg body weight infused intravenously once weekly (http://www.aldurazyme.com/pdf/az_us_hc_pi.pdf)
MPS II (Hunter disease)	Elaprase® (idursulfase)	0.5 mg/kg body weight infused intravenously once weekly (http://www.elaprase.com/pdf/Elaprase_V5.pdf)
MPS VI (Maroteaux-Lamy syndrome)	Naglazyme® (galsulfase)	1.0 mg/kg body weight infused intravenously once weekly (http://www.naglazyme.com/en/documents/Naglazyme_Prescribing_Information.pdf)

The dose regimens shown in Table 5 reflect those used in the clinical trials submitted for marketing approval of each agent. According to the Key Informants, there is significant interest in dose optimization, particularly determining a minimum effective dose for each disease, given the cost and burden on the family unit of weekly or fortnightly infusions. Several published studies (see findings for Guiding Question 3) have evaluated more than one dose regimen for some ERT products, including agalsidase alfa for Fabry disease;[49, 50] alglucerase[15, 51, 52] and imiglucerase[44, 53] for type I Gaucher disease; laronidase for MPS I;[54] idursulfase for MPS II;[55, 56] and galsulfase for MPS VI.[57]

Where and by whom is ERT administered?

In the U.S., ERT has typically been initially administered in an outpatient infusion clinic under the direction of a physician and team experienced in the use of these agents.[58] Such well-controlled settings are initially required to ensure immediate access to care to address serious infusion-associated adverse reactions, particularly immediate-type (IgE-mediated) hypersensitivity, or anaphylactic, events. Furthermore, medically fragile patients may more appropriately receive infusions in an inpatient or short stay infusion unit setting.[59]

Because these agents must be administered on a weekly or every other weekly basis for the life of the patient, ERT can be onerous, leading to missed school or workplace absence on the day it is received, and ultimately missed doses. To lessen the burden on patients and their families, some patients may be transitioned to home therapy.[20, 23, 60] Home infusion of ERT was initially studied in patients with type I Gaucher disease.[25, 61] It has been reported as an option for patients with Fabry disease,[24] MPS I,[22] and MPS II, and VI.[18, 20] However, patients with Pompe disease may not be able to transfer to home care because of an increased risk for serious adverse events during an infusion.[59] In general, the outcomes measured in these studies and the followup durations were similar to those reported by disease in the clinical trials summarized under Guiding Question 3. Safety was the main focus of most home infusion studies, as the patients had already been receiving ERT in a more controlled setting.

In the U.S., individual access to home therapy is typically determined by the patient's health insurance plan.[21] While the chronology may vary by patient and disease, transition to home therapy typically is considered after an initial 6 months of clinic treatment free from infusion-associated reactions.[18-20] Essential elements of a home infusion program include a home health care team, a defined protocol with careful patient selection, good vascular access either through a peripheral line or central access device, and a detailed management plan for infusion-associated reactions and anaphylaxis.[18, 19] An algorithm has been proposed for home infusion to treat MPS II, based on data from the international Hunter Outcome Survey.[62] This protocol commences ERT in clinic, with subsequent evaluation for home therapy. If successful, the patient is referred to a home care team for assessment, with agreement of all parties for transition, and followed by initiation of home treatment.[19] According to this approach, a patient who does not fulfill criteria for home therapy will continue treatment in clinic.

What adjunct treatments are used with each FDA-approved ERT product?

Therapeutic management of LSDs comprises measures that address specific symptoms of each disease, but offering no possibility for cure.[1-3, 5, 6] Similar organ-specific manifestations may appear in various combinations as a function of disease and disease stage, including the gastrointestinal tract, the central nervous system, the upper and lower respiratory tract, the visual system, the musculoskeletal system, and the hematopoietic system. For example, patients with Gaucher disease type I, the most common LSD, may develop hepatomegaly or splenomegaly, anemia, thrombocytopenia, impaired lung function, acute or chronic severe bone pain, avascular necrosis, and have growth impairment and pubertal delay.[7] Supportive care may then comprise a combination of generalized therapies that include blood transfusion, bed rest, analgesia, anti-inflammatory agents, hyperbaric oxygen, and surgery (e.g., splenectomy, orthopedic procedures), depending on severity and progression. The spectrum of management therapies is a function of each disease, its stage, and rate of progression.

In addition to disease-specific adjunct measures, a number of common drugs may used to prevent or treat infusion-associated reactions, some examples of which are shown in Table 6.[18] Dose regimens for antihistamines, corticosteroids and epinephrine are typically age-dependent, and may vary by physician choice, experience, or availability. Those presented in Table 6 have been reported in the context of home infusion of elaprase.[18] Given the common immune pathogenesis and physiology involved in infusion-associated reactions, and mechanism of action of the drugs, these treatments will be effective regardless of the ERT in question.

Table 6. Drugs used for the treatment of ERT infusion-associated reactions

Severity of Reaction	Antipyretic	Antihistaminic	Anti-inflammatory	Sympathicomimetic	H2 Receptor Antagonist
Mild	Acetaminophen Ibuprofen	Chlorpheniramine Hydroxyzine	NA	NA	NA
Moderate	Acetaminophen Ibuprofen	Chlorpheniramine (IV)	Hydrocortisone (IV)	NA	NA
Severe (anaphylaxis)	Acetaminophen Ibuprofen	Chlorpheniramine (IV)	Hydrocortisone (IV)	Epinephrine (IM) Albuterol (nebulized)	Ranitidine (IV)

IM = intramuscular; IV = intravenous; NA = not applicable;

Guiding Question 3: What published and unpublished studies have reported on the use and safety of this intervention?

Published Clinical Studies

We did not perform a systematic review of the literature for this Technical Brief; the primary goal was an environmental scan to show the relative scope and extent of studies that have been published since 1991. MEDLINE®, EMBASE®, and the Cochrane Controlled Trial database were searched electronically, as shown in Appendix A.

A total of 582 citations were identified in the searches. These comprised a total of 214 unique items for type I Gaucher disease; 147 for Fabry disease; 104 for glycogen storage (Pompe) disease; 51 for MPS I; 40 for MPS II; and, 26 for MPS VI. The volume of citations identified correlates roughly with the date of FDA marketing approval for the products for those diseases, although this relationship is not exact.

Among the 582 citations we identified, 238 were excluded at the title and abstract screen; 347 were retrieved electronically for full-text examination. We characterized the latter as follows: 116 review articles, 101 case series, 55 case reports, 52 prospective clinical studies (Phases I, II or III), 10 guideline reports, and 13 about which we were uncertain. We abstracted study details for 32 representative prospective clinical studies, selected as outlined in the Methods section of this Brief; an additional four extension studies are cited in Table 8;[43, 46] Table 9;[63] and Table 12.[57] All of these are organized according to disease and product, and arrayed in Table 7 through Table 12. Clinical outcomes reported in the studies, with the exception of harms, are shown in the tables. Details on the individual studies are provided in Appendix B.

Harms associated with ERT are reviewed under Guiding Question 1. Those are primarily infusion-related or immune-mediated. Among the clinical studies that were abstracted for Guiding Question 3 (Table 7 through Table 12), there were no reports of adverse events attributed to a pharmacodynamic effect of an ERT product. Long-term adverse sequelae of ERT have not been delineated for most products. Our Key Informants universally indicated the

adverse events they have observed were infusion-related or allergic type, not associated with pharmacodynamic actions of the glycoproteins themselves.

Fabry Disease

Characteristics of seven international studies of agalsidase alfa and beta therapy for Fabry disease[39, 41, 49, 50, 64-66] are summarized in Table 7. A total of 273 patients with mild-to-moderate symptoms including impaired renal function, cardiac involvement, cerebrovascular infarction, bone pain and other symptoms were enrolled. Patients ranged in age from as young as 9 years [41] to 76 years[66] with length of followup ranging from 10 weeks[49] up to 234 weeks.[40] ERT doses ranged from 0.1 mg/kg weekly to 1.0 mg/kg every other week (fortnightly). Outcomes varied by study, including plasma substrate level, renal function, cardiac function, cerebrovascular disease, pain, growth, and quality of life. Plasma substrate levels and capillary substrate inclusions were linked to renal, cardiac and cerebrovascular endpoints in one randomized, placebo-controlled trial.[39] Two studies evaluated multiple dose regimens of agalsidase alfa.[49, 50]

Gaucher Disease

Table 8 shows results from eight trials of ERT (alglucerase, imiglucerase, velaglucerase) for type I non-neuronopathic Gaucher disease. Four studies were performed in the U.S.,[15, 45, 51, 52] four were international.[43, 44, 46, 53] A total of 265 patients with mild-to-moderate symptoms including anemia, thrombocytopenia, hepatomegaly, splenomegaly, and early bone lesions were enrolled. They ranged in age from as young as 2 years[52] to 75 years[53] with length of followup ranging from 18 weeks[43] to 208 weeks.[45] Doses ranged from 3.5 IU/kg weekly [53] to 60 IU/kg fortnightly.[15, 43-46, 51, 52] Outcomes varied by study, including primarily hematological measures (e.g., anemia, thrombocytopenia), hepatomegaly, splenomegaly, and skeletal abnormalities. Different dose regimens were evaluated in two nonrandomized studies of alglucerase[51, 52] and two randomized trials involving imiglucerase.[44, 53]

Glycogen Storage Disease (Pompe Disease)

Eight studies of ERT (alglucosidase alfa) for glycogen storage disease (Pompe disease) are summarized in Table 9.[63, 67-73] Two are categorized as randomized trials.[68, 70] Two studies were performed in the U.S.[70, 71] A total of 230 patients, 139 with the juvenile/adult form,[67-69] and 91 with infantile Pompe disease[63, 70-73, 80] were enrolled, ranging in age from 1 month[73] to 70 years.[68] Adult or juvenile patients mostly had moderate-to-severe disease manifested by respiratory impairment, myopathy and reduced muscle strength, and impaired mobility.[67-69] Patients with infantile Pompe disease had severe manifestations marked by left ventricular hypertrophic cardiomyopathy, profound muscle weakness and hypotonia, and ventilator dependency.[64-68, 72] Across all studies, ERT was infused at doses ranging from 10 to 40 mg/kg, weekly or fortnightly. One study evaluated two different dose regimens of alglucosidase alfa.[70] Outcomes varied by study, and type of disease, with cardiac, pulmonary, and muscle function being the most common measures.

MPS I (Hurler Disease)

Table 10 shows summaries of four clinical studies of α-L-iduronidase (laronidase) therapy that enrolled a total of 138 patients with severe or attenuated forms of MPS I (Hurler disease).[54, 74-76] None of the studies was performed solely in the U.S. Patients ranged in age from as young as 1 year[54, 76] to 43 years.[74, 75] Symptoms ranged from mild to severe, including impaired

Table 7. Selected clinical trials of agalsidase alfa and agalsidase beta for the treatment of Fabry Disease

Author, Year, Country, Sample Size	ERT	Study Design	Treatment Groups and Dose	Disease Stage/Type	Age at study onset Mean (range) yrs	Length of follow-up (wks)	Substrate level	Renal function	Cardiac function	Pain scores	Cerebrovascular	Growth	Quality of life
Clarke,[49] 2007, international, 1) n=4 2) n=4 3) n=4 4) n=3 5) n=3	agalsidase alfa	open label, randomized, dose optimization trial	5 treatment groups: 1) 0.1 mg/kg weekly 2) 0.2 mg/kg eow, 3) 0.2 mg/kg weekly 4) 0.4 mg/kg eow 5) 0.4 mg/kg weekly	treatment groups had comparable baseline substrate levels	1) 28 (16-36) 2) 38 (33-41) 3) 25 (20-32) 4) 23 (21-25) 5) 28 (26-30)	10	●						
Wraith,[41] 2008, international, N=16	agalsidase beta	open label study in children	all agalsidase beta 1 mg/kg eow	symptomatic	12 (9-12)	48	●	●	●			●	●
Banikazemi,[39] 2007, international, agalsidase β: 51 placebo: 31		randomized double blind, placebo controlled trial	agalsidase β 1 mg/kg eow vs. placebo	symptomatic	agalsidase β: 47 (SD: 10) placebo: 44 (SD: 9)	up to 152		●	●		●		
Germain,[40] 2007, international, N=58		open label extension study	agalsidase β 1 mg/kg eow	symptomatic	31 (17-62)	up to 234	●	●	●	●			
Eto, 2005,[64] Japan, N=13		open label phase II bridging study	agalsidase β 1 mg/kg eow	symptomatic	27 (16-34)	20	●	●					

Table 7. Selected clinical trials of agalsidase alfa and agalsidase beta for the treatment of Fabry Disease (continued)

Author, Year, Country, Sample Size	ERT	Study Design	Treatment Groups and Dose	Disease Stage/Type	Age at study onset Mean (range) yrs	Length of follow-up (wks)	Substrate level	Renal function	Cardiac function	Pain scores	Cerebrovascular	Growth	Quality of life
Vedder,[50] 2008, Netherlands, 1) 18 2) 13 3) 21	agalsidase alfa and agalsidase beta	dose optimization study	3 treatment groups: 1) 0.2 mg/kg alfa eow 2) 0.2 mg/kg beta eow 3) 1.0 mg/kg beta eow	no information provided	1) 47 (19-62) 2) 49 (25-73) 3) 48 (27-70)	52	●	●	●				
Vedder,[66] 2007, Netherlands, 1) 18 2) 16		open label randomized, controlled trial	2 treatment groups: 1) 0.2 mg/kg eow alfa 2) 0.2 mg/kg eow beta	treatment groups stratified by disease severity	1) 42 (19-60) 2) 48 (24-76)	52-104	●	●	●	●			

Table 8. Selected clinical trials of alglucerase, imiglucerase, and velaglucerase for the treatment of Gaucher Disease Type I

Author, Year, Country, Sample Size	ERT	Study Design	Treatment Groups and Dose	Disease Stage/Type	Age at study onset Mean (range) yrs	Length of follow-up (wks)	Anemia, thrombocyte	Liver size	Spleen size	Skeletal pathology	Physical score	Mental score
Altarescu,[51] 2000, United States 1) N = 12 2) N = 32	alglucerase	dose optimization study	1) 60 IU/kg eow, reduced to 30 IU/kg, then reduced to 15 IU/kg 2) 10 IU/kg eow	symptomatic	1) range 7-58 2) range 9-69	1) 104 2) 52	●	●	●			
Pastores,[52] 1993, United States N=33		open label, dose optimization study	30 IU/kg vs. 40 IU/kg, vs. 50 IU/kg, vs. 60 IU/kg eow	symptomatic	32 (2-63)	26-104	●	●	●	●		
Kishnani,[44] 2009, international 1) N=33 2) N=62	imiglucerase	open label, randomized, phase IV, dose frequency trial	2 treatment groups: 20-60 IU/kg 1) monthly dose fortnightly 2) monthly dose every 4 weeks	at least 2 yrs on imiglucerase	age at initial imiglucerase infusion: 1) 36 (10-74) 2) 42 (11-75)	104	●	●	●	●	●	●
Sims,[45] 2008, United States N=33		open label, single cohort prospective study	60 IU/kg eow	symptomatic	median 43 (12 -70)	208	●	●	●	●		
de Fost,[53] 2007, Netherlands 1) N=5 2) N=6		randomized, controlled trial	2 treatment groups: 1) 3.45 IU/kg weekly or 7.5 IU/kg eow 2) 15 IU/kg every 4 weeks	symptomatic	overall 51 (34-75)	52	●	●	●			
Grabowski,[15] 1995, United States 1) N=15 2) N=15	alglucerase imiglucerase	randomized, double-blind, parallel trial	2 treatment groups: 1) alglucerase 60 IU/kg eow 2) imiglucerase 60 IU/kg eow	symptomatic	1) 28 (12-52) 2) 39 (13-69)	39	●	●	●			

Table 8. Selected clinical trials of alglucerase, imiglucerase, and velaglucerase for the treatment of Gaucher Disease Type I (continued)

Author, Year, Country, Sample Size	ERT	Study Design	Treatment Groups and Dose	Disease Stage/Type	Age at study onset Mean (range) yrs	Length of follow-up (wks)	Anemia, thrombocyto-	Liver size	Spleen size	Skeletal pathology	Physical score	Mental score
Elstein,[43] 2011 Israel (same study population as Zimran 2010[46]	velaglucerase alfa	open label, Phase I/II study with extension	60 IU/kg eow	symptomatic	extension: 39 (18-62)	I/II: 39 extension: up to 208	●	●	●	●		
Zimran,[46] 2010, Israel (same study population as Elstein 2011[43]) phase I/II: N =11 extension: N =8		open label, Phase I/II study with extension	60 IU/kg eow tapered to 30 IU/kg eow	symptomatic	phase I/II: 41 (18-69)	I/II: 39 extension: up to 208	●	●	●			

Table 9. Selected clinical trials of alglucosidase alfa for the treatment of glycogen storage disease (Pompe Disease)

Author, Year, Country, Sample Size	Study Design	Treatment Groups and Dose	Disease Stage/Type	Age at study onset Mean (range) yrs	Length of follow-up (wks)	Enzyme level	6-min walk test	Pulmonary function	Cardiac function	Muscle function	Quality of life	Survival
Orlikowski,[67] 2011, France N=5	open label study in adults	20 mg/kg eow	juvenile/adult form	48 (28-62)	52	●		●		●	●	
van der Ploeg,[68] 2010, international 1) N=60 2) N=30	randomized, double-blind, placebo controlled trial	1) treatment: 20 mg/kg eow 2) Placebo	juvenile/adult form	treatment: 45 (16-70) placebo: 43 (12)	78		●	●		●		
Strothotte,[69] 2010, Germany N=44	open label study	20 mg/kg eow	juvenile/adult form	49 (21-69)	52	●	●	●		●		
Kishnani,[70] 2009, United States N=16	open label randomized trial extension to Kishnani, 2006[63]	20-40 mg/kg eow	infantile form	mean age at end of study: 3 (2-4)	60-150			●	●	●		●
Nicolino,[71] 2009, United States N=21	open label study	20-40 mg/kg eow	infantile and juvenile form	mean age (in months): 16 (4-43)	up to 168			●	●	●	●	●
Levine,[72] 2008, international N=8	open label, Phase II trial for children, extension study to Kishnani 2006[63]	10-20 mg/kg eow	infantile form	mean age (in months): 6 (3-15)	52			●	●			
McDowell,[73] 2008, international 1) N=7 2) N=31	retrospective study on patients who were in open label trial for children	1) patients with arrhythmias 2) patients without arrhythmias dose not reported	infantile form	1) median (in months): 7 (6-13) 2) median (in months): 8 (1-43)	78				●			
Kishnani,[63] 2006, international N = 8	Phase II, open label study in children	10-20 mg/kg weekly or 20 mg/kg eow	infantile form	median age (in months) at first treatment: 5 (3-15)	up to 153			●	●	●		●

Table 10. Selected clinical trials of laronidase for the treatment of Mucopolysaccharidosis I (Hurler Disease)

Author, Year, Country, Sample Size	Study Design	Treatment Groups and Dose	Disease Stage/Type	Age at study onset Mean (range) yrs	Length of follow-up (wks)	Substrate level	Liver volume	6-min walk test	Range of motion	Mental development	Pulmonary function	Cardiac symptoms	Sleep apnea	Visual acuity	Growth
Clarke,[74] 2009, international N=40	open label extension study to Wraith et al, 2004[75]	100 U/kg weekly	attenuated	16 (6-43)	182	●	●	●	●	●	●		●	●	
Giugliani,[54] 2009, international 1) N=8 2) N=8 3) N=8 4) N=9	dose optimization trial	1) 100 IU/kg weekly 2) 200 IU/kg eow 3) 200 IU/kg weekly 4) 300 IU/kg eow	severe (n=10) and attenuated (n=23)	overall: 9 (1-21) 1) 8 (3-17) 2) 9 (5-17) 3) 9 (1-20) 4) 9 (4-21)	26	●	●	●							
Wraith,[76] 2007, international N=20	open label study or children <5 yrs of age	100-200 IU/kg weekly	severe (n=16) and attenuated (n=4)	3 (1-5)	52	●	●			●		●	●		●
Wraith,[75] 2004, international laronidase: N=22 placebo: N=23	Phase III randomized, double-blind, placebo-controlled trial	100 IU/kg weekly vs. placebo	severe (n=1) and attenuated (n=44)	laronidase: 16 (7-43) placebo: 15 (6-39)	26	●	●	●	●		●		●		

pulmonary function, left-ventricular hypertrophy, hepatomegaly, impaired mobility, impaired growth, sleep apnea, and decreased functional quality of life reflected by the Child Health Assessment Questionnaire/Health Assessment Questionnaire disability index. Doses of laronidase ranged from 100-200 IU/kg weekly to 300 IU/kg fortnightly, with length of followup ranging from 26 weeks[54, 75] to 182 weeks.[74] One study was reported as a randomized, open-label dose-optimization trial using three alternative regimens, shown in Table 10.[54] Outcomes varied by study, most commonly including plasma substrate level, liver volume, 6-minute walk test, and sleep apnea.

MPS II (Hunter Disease)

Three clinical studies of idursulfase therapy summarized in Table 11 enrolled a total of 188 patients with attenuated MPS II (Hunter disease).[55, 56, 77] One was performed in the U.S.[55] Patients ranged in age from 6[55, 56] to 54 years,[77] with symptoms of MPS II, including hepatosplenomegaly, radiographic evidence of dystosis multiplex, cardiomyopathy, valvular heart disease, joint mobility, and evidence of upper airway obstruction. Two studies were randomized, placebo-controlled trials that evaluated idursulfase in several dose regimens ranging from 0.15 mg/kg weekly to 1.5 mg/kg fortnightly.[55, 56] Length of followup ranged from 24 weeks[55] to 53 weeks.[56] Outcome measures varied by study, but most commonly included the 6-minute walk test and pulmonary function.

MPS VI (Maroteaux-Lamy Disease)

Table 12 shows two international clinical studies of galsulfase in a total of 179 enrolled patients to treat symptomatic or rapidly progressive MPS VI (Maroteaux-Lamy syndrome).[78, 79] Symptoms included impaired pulmonary function, impaired walking ability, impaired joint range of motion, skeletal dysplasia, joint stiffness and pain, hepatosplenomegaly, and impaired visual acuity. Patient age ranged from 5 to 29 years.[78] Galsulfase was administered at 0.2-1.0 mg/kg weekly, with followup ranging from 48 weeks[79] to 240 weeks.[78] The primary outcome of the 2010 Harmatz study[78] was long-term pulmonary function and growth. The 2005 Harmatz study reported liver volume, 6-minute walk test, joint range of motion and other outcomes.[79]

Published Registry Studies

Summaries of published registry studies of ERT for Fabry, type I Gaucher, and Hunter's disease are shown in Appendix C. These generally show the same outcomes as reported in the clinical trials summarized, previously. However, the actual percentages of outcomes associated with each disease and its treatment may not be as informative as possible, given uncertainty in the real denominators (patient numbers) associated with each registry as participation is voluntary.

Unpublished Studies and Ongoing Clinical Trials

For this Technical Brief, the ERT product manufacturers supplied the EPC with compilations of information that included abstracts and posters presented at scientific meetings, as well as product bibliographies and monographs. We cross-indexed the bibliographies we received with published literature identified in our search as well as through NCBI PubMed®. In this exercise,

Table 11. Selected clinical trials of idursulfase for the treatment of Mucopolysaccharidosis II (Hunter Disease)

Author, Year, Country, Sample Size	Study Design	Treatment Groups and Dose	Disease Stage/Type	Age at study onset Mean (range) yrs	Length of follow-up (wks)	Substrate level	Liver volume	6-min walk test	Range of motion	Pulmonary function	Cardiac symptoms	Sleep apnea
Okuyama,[77] 2010, Japan idursulfase: N=10	open label study in adults	0.5 mg/kg weekly	attenuated	30. (21-54)	52	●	●	●	●	●	●	●
Muenzer,[55] 2007, US idursulfase: N=9 placebo: N=3	Phase I/II, randomized, double-blind, placebo-controlled trial	3 treatment groups: 1)0.15 mg/kg eow 2) 0.5 mg/kg eow 3) 1.5mg/kg eow 4) placebo	attenuated	overall: 14 (6-20) 1) 11 (9-14) 2) 20 (20) 3) 8 (6-10) 4) 17 (13-20)	trial: 24 extension: 26	●	●	●	●	●	●	●
Muenzer,[56] 2006, international 1) idursulfase: N=32 2) idursulfase: N=32 3) placebo: N=32	Phase II/III, randomized double-blind, placebo-controlled trial	3 treatment groups: 1) 0.5 mg/kg weekly 2) 0.5 mg/kg eow 3) placebo	treatment groups had same distribution baseline disease scores from 2-6	1) 15 (6-26) 2) 14 (5-31) 3) 13 (5-29)	53			●		●		

Table 12. Selected clinical trials of galsulfase for the treatment of Mucopolysaccharidosis VI (Maroteaux-Lamy Syndrome)

Author, Year, Country, Sample Size	Study Design	Treatment Groups and Dose	Disease Stage/Type	Age at study onset Mean (range) yrs	Length of follow-up (wks)	Liver volume	6-min walk test	Range of motion	Pulmonary function	Ophthalmologic evaluation	Sleep apnea	Growth
Harmatz,[78] 2010, International 1) galsulfase: N=7 2) galsulfase: N=123 3) galsulfase: N=39	extension study to Phase I/II, II, III trials reporting results up to 48 weeks, Harmatz, 2004[57]	1) 0.2 mg/kg or 1.0 mg/kg weekly 2) 0.2 mg/kg weekly 3) 0.2 mg/kg weekly	symptomatic	phase I/II: 12 (7-16) phase II: 12 (6-21) phase III: 14 (5-29)	up to 240				●			●
Harmatz,[79] 2005, international galsulfase: N=10	open label study	1.0 mg/kg weekly	rapidly advancing disease	13 (6-22)	48	●	●	●		●	●	●

our team did not identify key information we had not already found in the course of this project in published studies, review articles, FDA documents, Key Informant interviews, or manufacturers or advocacy websites.

Appendix D shows 29 current clinical studies (Phase I-IV) identified through a search of the Clinicaltrials.gov website. These are being performed for all ERT products, with similar endpoints and outcomes as reported in this Technical Brief. Notably, two studies (NCT0638547, NCT 00852358) are evaluating intrathecal administration of laronidase to treat CNS symptoms of MPS I (Hurler's disease). Two studies (NCT00920647, NCT 01506141) are evaluating intrathecal administration of idursulfase to treat CNS symptoms of MPS II (Hunter's disease).

Guiding Question 4: What are key unresolved or controversial issues with ERT in LSDs?

We sought to address this Guiding Question through integration of information from published clinical studies, narrative review articles, FDA summary documents, and a series of semi-structured interviews with five highly experienced Key Informant physicians and end-users of ERT. The complete discussions are not summarized; rather, we present key clinical concurrences.

Key Informant Semi-structured Telephone Interviews

The Key Informants universally asserted that neuronopathic aspects of any LSD do not respond to ERT, because the large glycoproteins do not penetrate the blood-brain barrier. One proposed approach to overcome this obstacle is direct intrathecal administration of ERT products. Our literature scan identified two case reports on the intrathecal approach, one in a patient with MPS I,[81] the other a patient with MPS VI.[82] Intrathecal administration of ERT is the subject of current clinical studies in patients with MPS I or MPS II (see Appendix D). Alternatively, according to some Key Informants, neuronopathic Gaucher disease may, in theory, be treated using a combination of ERT with substrate inhibition using small molecules that cross the blood-brain barrier, for example miglustat, and an ERT product indicated for Gaucher disease. However, we did not find any published reports on this approach, and neither miglustat nor any ERT product for Gaucher disease has received FDA marketing approval for this purpose.

In our discussions, the Key Informants indicated ERT has no effect on CNS manifestations of Fabry disease and does not reverse established disease-associated renal or cardiac damage. Renal or cardiac function outcomes were investigated in six clinical studies cited in Table 7. One randomized trial cited in Table 7 reported cerebrovascular outcomes in Fabry patients who received ERT.[39] While liver and spleen manifestations of the MPS family respond well to ERT or perhaps may be prevented, pre-existing cardiopulmonary damage is difficult to resolve. Cardiac and pulmonary function outcomes have been studied and reported for MPS I, II, and VI (Table 10 through Table 12). The Key Informants reported Pompe disease is difficult to treat with ERT, with earlier initiation better than later in adults, but of lesser benefit in the infantile form.

According to our Key Informants the optimal time to initiate ERT is unknown for any LSD, although they suggest earlier is better to prevent the development of irreversible organ and tissue damage. We identified a few published clinical studies that investigated the timing of ERT relative to symptom onset and clinical outcomes for a few LSDs. These include renal function and disease progression in adult patients with Fabry disease treated with agalsidase beta;[83] and,

avascular necrosis and other manifestations of type I Gaucher disease.[84, 85] Several published clinical studies, mainly from China, have investigated the impact of early initiation of ERT in infants with Pompe disease.[70, 86-90] The views expressed by the Key Informants are consistent with those expressed in the literature and review articles based on current evidence.[5, 6, 8-12, 59, 91] However, this question has not been systematically investigated in controlled trials.

Besides the examples given above, a number of other unresolved questions were specifically voiced by the Key Informants, as follow:

- Because there are no tools to know how diseases will progress, how aggressive should physicians be with treatment?
- What is the minimum effective dose of any ERT for a specific disease?
- Are there any reliable biomarkers available for clinicians to optimize therapy?
- What is the mechanism of action of ERT at the molecular level?

Patient Advocate Telephone Interviews

Two individuals participated in these interviews, a patient with an LSD and a caregiver of a patient with a LSD. The discussion touched on a variety of issues including clinical outcomes of importance to patients and parents; the importance of "community" in ongoing ERT; information of importance to patients and caregivers; bone marrow transplantation; and, the influence of disease on family members.

The patient with LSD described important clinical outcomes as including joint range of motion, ability to walk, increased energy and feeling of well-being, and independence in daily living. The patient further described how ERT stabilized cardiac function; improved airway patency, lung capacity, and bone health; and, reduced immune suppression-related infections. These types of improvements were of great significance in the patient's view because they directly affect the quality of life, an outcome that has been studied in patients with type I Gaucher disease,[92-94] Fabry disease [95] and Hurler disease.[96] This patient noted that a shortage-related ERT hiatus resulted in rapid loss of cognitive function and energy, and led to bone aching and pain, all of which improved with resumption of ERT. A similar sequence of events was reported in 2011 among a group of 50 adult type I Gaucher disease patients in Spain during a 6-month shortage of imiglucerase secondary to viral contamination and manufacturing problems in Europe;[97] a similar situation occurred in Australia in 2009.[98] The patient with LSD noted having a degree of "guilt" about use of substantial healthcare resources in times of shortage.

The caregiver described the patient under care as full of energy on ERT, social, and no longer readily identifiable (from a distance) as having an LSD. The caregiver further indicated the patient's doctor has discussed hematopoietic stem-cell transplantation as an option, but cautioned it would not necessarily stabilize cognitive function, carries a high risk of harms, and may not yield any more improvement than ERT. The caregiver also indicated the community aspect of hospital-based therapy as important to a family sense of well-being.

Summary and Implications

This Technical Brief addresses four Guiding Questions to examine the state of evidence on the use of ERT in patients with an LSD for which an FDA-approved product is available. To address Guiding Questions 1 and 2, we summarized indications and dose regimens from the FDA-approved prescribing information for each product, as well as information from review articles on how, where, and by whom ERT may be administered. Results summarized under Guiding Question 3 provide a picture of clinical and registry studies for each product, from an environmental scan of the published literature. Guiding Question 4 integrates information from a series of semi-structured interviews with five highly experienced Key Informant physicians and end-users of ERT, relevant published clinical studies, narrative review articles, and FDA summary documents. The information compiled in this Brief is intended as a resource with which health care providers and decision-makers may educate themselves about the ERT products available, how they are used, and clinical issues articulated by clinical experts and patient advocates.

Given the rarity of these diseases individually, there are few substantial randomized, controlled, clinical trials; instead, the evidence base comprises a few small randomized, controlled trials, cohort studies, prospective single-arm studies, case series, case reports, and registry summaries. As expected, the volume of published literature correlates roughly with the FDA marketing approval dates, starting with the first agent, alglucerase, for type I Gaucher disease in 1991. Thus, about 37 percent of the articles we identified in our scan were about ERT (all three available products) in type I Gaucher disease, which was followed by articles on Fabry disease, which comprised 25 percent of the literature volume. The other 4 LSDs together make up about a third of the published articles we found.

The selected clinical studies summarized in the Brief map the characteristics of available evidence, including patient populations, sample size, study methods, and what outcomes have been reported for each product. Across the six LSDs, as outlined in Table 1, and clinical studies (Table 7 through Table 12) the reported patient characteristics are highly heterogeneous, as each exhibits a disease-specific constellation of signs and symptoms. Further, the expression of symptoms often varies greatly among and within the six diseases, ranging from early infancy for Pompe disease to perhaps mid-adulthood for type I Gaucher disease. However, some commonalities in symptoms clearly exist between these LSDs: for example hepatomegaly or splenomegaly, bone and other skeletal abnormalities, abnormal hematological measures (anemia, thrombocytopenia), cardiac dysfunction, pulmonary dysfunction, and impaired ambulation.

The conundrum of these orphan diseases is that they are very rare and genetically unique within and between types; however, because the macromolecular storage compounds accumulate within lysosomes—which are found in every cell type in the body—they can exhibit strikingly similar individual pathologies. Yet, each ERT product is effective for only one LSD, and ERT outcomes may vary among patients with the same disorder. These inconsistencies may complicate decision-making as it relates to initiating ERT—when is the optimal time? The majority of clinical studies we examined for this Brief did not address this issue; all patients in studies we summarized were symptomatic, to a greater or lesser degree, and required therapy. However, several of the Key Informants indicated that timing of treatment is very important as it relates to disease progression and development of irreversible damage. We identified a few reports that showed the effect of early initiation of agalsidase beta on renal function and disease progression in adult patients with Fabry disease.[83] Others reported the impact of early ERT on manifestations of type I Gaucher disease.[84, 85] Finally, several published clinical studies, mainly

from China, have investigated the impact of early detection and initiation of ERT in infants with Pompe disease.[70, 86-90]

Information contained in several sources, including the FDA-approved label for each product; narrative and systematic reviews; clinical studies; and, Key Informant interviews suggests that ERT agents have few, if any, specific adverse effects on recipients. The vast majority of adverse events are infusion-associated reactions, which are generally mild and easily controlled or self-limiting. Immune sensitization and anaphylactic responses have been reported; the former may rarely affect therapy, whereas the latter will usually preclude further administration of the specific agent and are the subject of FDA-mandated Black Box warnings on the approved label for alglucosidase alfa (Pompe disease), laronidase (Hurler disease), and idursulfase (Hurler disease).

Our scan of the literature, the Key Informant discussions, and other publicly available information revealed a number of unanswered questions with regard to clinical use of the agents; for example, optimal dose regimens have not been established. Several articles cited in Table 8 reported dose optimization studies for alglucerase [51, 52] and imiglucerase [44] in patients with type I Gaucher disease, investigating variation of the amount of product administered or frequency of administration. There are many other clinical reports, editorials, and commentaries on this issue, dating back to the mid-1990s soon after the first ERT product for type I Gaucher disease became commercially available.[37, 38, 51, 99-107] We also identified reports on the effect of dose variation for ERT in patients with Fabry disease[66, 108] and MPS I.[54] The evidence base is substantially more robust for type I Gaucher disease than for the others, as would be expected given the relative prevalence of these diseases and the chronology of FDA marketing approvals.

The pharmacodynamic mechanism of action of ERT agents is not well understood, how they are taken up by lysosomes, and how they are distributed into various compartments and tissues.[5] This bears directly on clinical outcomes of ERT in organs or compartments that are less accessible to large glycoproteins. For example, the blood-brain barrier represents a significant impediment that limits the utility of ERT for diseases that have a neuronopathic component. This obstacle may ultimately be surmounted, perhaps, with the use of combined therapy comprising small molecule substrate inhibitors (e.g., miglustat) or chaperone molecules, combined with ERT, or perhaps with intrathecal administration of enzymes.[27-29, 33, 34] However, chaperone therapy is deemed investigational at present, and combined ERT and SRT is not yet well studied.

In considering the implications of this Technical Brief, the issues are not merely technical or clinical. While patients with so-called "classic" symptoms of a LSD can be apparent, atypically presenting patients often require greater consideration.[109] It is unclear whether it is appropriate to initiate ERT in an asymptomatic individual, including those in whom a genetic mutation specific for a LSD has been identified, because the disease genotype-phenotype relationship is not exact.[109-111] Furthermore, the phenotypic expression of a LSD may significantly vary among individuals; it may not express itself at all or, symptoms may not manifest for a very long period of time.[3, 62]

As discussed above, the appropriate time to start ERT has been investigated in clinical studies for several LSDs. By contrast, information concerning whether or when to stop ERT is far less clear. In our Key Informant interviews, we heard anecdotally of experience where the burden of therapy on the family of a patient with a rapidly progressing or nonresponsive LSD drove a decision to cease and turn to supportive comfort care alone. This raises complex questions related to the psychosocial dynamics of the family unit and also around the ethics of treatment withdrawal. We did not identify clinical studies of this issue, but it is reasonable to

envision disease registries as storehouses and conveyances for this type of information to physicians. While registry data do not generally permit clinical conclusions as to the effectiveness and safety of ERT, they do represent a source of long-term longitudinal data on those outcomes and could collect information related to treatment cessation and the parameters used to make such determinations. However, we are not aware of existing registry data on this topic.

The rarity of the LSDs in typical primary care or pediatric practice, and thus physician recognition and timely initiation of ERT, is a topic that has not been well-studied.[112, 113] In the U.S., the National Organization for Rare Disorders and the National Institutes of Health Office of Rare Diseases, estimate that 25 million Americans suffer from a rare disease.[113] While the latter seems a large number, the LSDs considered in this Technical Brief are individually very rare. Clinical vigilance therefore becomes key to ensure timely initiation of ERT for LSDs.[110] Primary care physicians—who typically manage common problems in unselected patients—must recognize the occasional zebra in a herd of horses, without working up every horse, because common patients can present with rare diseases.[114]

A generic primary care practice approach to patients with rare disease has been published.[113] According to the authors, this approach may reduce problems that include a lack of coordinated care, lack of information about rare diseases, delayed diagnosis, and delayed therapy.[113] The authors of this paper further suggest this approach may ultimately enable primary care physicians to systematically address the problems posed by individuals who present with an unrecognized or rare disorder, presumably including an LSD. Once an LSD is diagnosed, a comprehensive treatment plan can be developed involving a multidisciplinary team headed by a biochemical geneticist or other physician experienced in treating these disorders, early in its course before irreversible damage has occurred.

Next Steps

Many questions remain about ERT, despite the fact that some of the agents have been commercially available since the early 1990s. While this list is not complete, several key areas of study were identified by our scan of the published literature and other information sources, and our discussions with Key Informants:

- **Pharmacodynamic and Pharmacokinetic Issues**

While we did not review published studies along these lines of investigation, several Key Informants suggested the need for basic research on the mechanism of action of ERT products, and to improve cellular targeting, uptake, and pharmacokinetic parameters. Improved ERT product formulations have significant potential to enhance therapeutic effectiveness and safety. Molecular modifications designed to increase enzyme delivery to minimally or nonaccessible physiologic compartments would have significant therapeutic benefit. This would particularly benefit patients with diseases that affect the CNS and are not treatable with current agents, and diseases that cause bone lesions and damage, which do not respond well to ERT due to limited uptake into those sites. In theory, depot products, similar to those developed for intravenous immune globulin therapy, with subcutaneous administration and prolonged release, would potentially ease the burden of therapy on patient and family alike by simplifying administration.

- **ERT Dose Regimen Optimization**

A majority of our Key Informants agreed that optimal ERT dose regimens are not known for any of the LSDs, although as discussed above in this Brief, some information is available in the literature on this topic. Ideally, comparative randomized dose studies using standardized protocols would address dose optimization for all indications. This question bears on issues that include clinical effectiveness, resource utilization, and patient compliance.

- **Early Treatment Initiation**

Our Key Informants generally agreed that the earliest possible initiation of ERT, prior to or at first appearance of symptoms, is necessary to reap the most benefits by preventing or delaying irreversible tissue damage with disease progression. Early treatment initiation is predicated on a high level of clinical vigilance on the part of primary care and pediatric physicians to recognize the possible presence of an LSD based on perhaps subtle signs, family history, and clinical experience, and to make prompt referrals to specialists. Any clinical study involving withholding treatment to study the effect of ERT timing on clinical outcomes would be unethical. The impact of early initiation of ERT for a few diseases has been reported, as outlined previously in this Brief.

All these endeavors will require the combined efforts of physician investigators, bench scientists, pharmaceutical manufacturers, and patient advocacy groups. Given the individual rarity of the LSDs, patient accrual for clinical studies is difficult. Ideally, cooperative efforts—perhaps analogous to the Children's Oncology Group—may provide a pathway toward ensuring that studies are standardized in conduct and reporting. Disease-specific registries, with standardized operating procedures for data submission and reporting will remain important to enhance knowledge of natural history and therapeutic outcomes. Such efforts would hasten referrals to specialists in metabolic disease, obviously benefitting patients and their families, but also potentially benefitting the overall health care system as the result of earlier care and reduced disease morbidity.

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