

Evidence-based Practice Center Technical Brief Protocol

Project Title: Enzyme Replacement Therapy for Lysosomal Storage Disorders

Amendment Date(s) if applicable: August 28, 2012

(Amendments Details—see Section VII)

I. Background and Objectives

Lysosomal storage disorders (LSD) comprise a group of inherited metabolic diseases (IMD) that occur secondary to genetic defects (eg, single substitutions, gene deletions) that result in the deficiency of enzymes that are needed in the catabolism of a number of biological macromolecules in lysosomes.¹⁻³ These enzyme deficiencies cause substrates to accumulate within connective tissue, skeletal structure, and organs, resulting in progressive damage. LSDs are broadly divided into groups based on the nature of the stored substrate: mucopolysaccharidoses (MPS), lipidoses, glycogenoses, and oligosaccharidoses. LSDs are rare, with an estimated combined incidence of 1 in 1,500 to 7,000 live births. Some 50 different LSDs have been identified.³

For a majority of LSDs, therapeutic management consists of symptomatic care of disease manifestations, with no possibility for cure. Supportive care measures are disease specific, depending on the organs involved and degree of physical impairment. For example, patients with Gaucher's Disease Type I, the most common LSD, may develop visceral problems (hepatomegaly, splenomegaly), anemia, thrombocytopenia, lung disease, severe bone pain (acute or chronic), avascular necrosis, and have growth impairment and pubertal delay.⁴ 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). However, the advent of enzyme replacement therapy (ERT) offers an alternative to traditional management practices.⁵⁻⁹

The principle of ERT is to replace specific defective enzymes in LSD patients with in vitro synthesized functional enzymes. ERT products are administered by intravenous infusion, dosages determined by patient body weight, usually every other week, for the life of the patient. This approach is not curative. The infused enzymes are taken up by cells, into lysosomes, where they catabolize the substrates that have accumulated. Clinical outcomes potentially affected by ERT include survival, quality of life and ability to perform activities of daily living, cognitive development and function, neurodevelopmental function, and disease-specific symptomatic relief.

Currently, there are six ERT products that have received FDA marketing approval in the United States. Each is specific for a single disease: mucopolysaccharidosis I (Hurler disease), mucopolysaccharidosis II (Hunter disease), mucopolysaccharidosis VI (Maroteaux-Lamy syndrome), Fabry's disease, Gaucher Type I, and Pompe disease (see

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Table). Accordingly, this report will focus on those six LSDs. These diseases in general do not have central nervous system manifestations, although this may vary by the severity of disease expression.

The objective of this technical brief is to provide an overview of the current state of FDA-approved ERT for the treatment of lysosomal storage disorders. The overview will present the clinical indications for each ERT, the potential benefits and harms associated with each ERT, and dosing and administration details of each ERT. This brief will also provide a discussion of the key unresolved or controversial issues surrounding the use of ERT to treat lysosomal storage diseases.

II. 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? Provide a state of the current research for the following information on available studies:

- 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 follow up
- g. Outcomes measured

h. Adverse events/harms/safety issues reported

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

III. Methods

Several sources will be used to inform this technical brief. Information will be 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 above will rely on information from published narrative reviews, clinical guidelines and information in the grey literature. The latter will include information culled from pharmaceutical companies, patient advocacy groups, and other sources as identified in an internet search.

Guiding Question 3 will be addressed through a review of the literature. Key Informants will provide guidance on the potential clinical outcomes of interest and the potential benefits and harms of ERT as the review is implemented.

Guiding Question 4 will rely on integrating information from Key Informants, grey literature, and narrative reviews.

1. Data Collection

A. Discussions with Key Informants

The Key Informants include both content experts as well as patients. The content experts will include medical directors, pediatricians, neurologists, geneticists, and specialists in metabolic diseases, lysosomal storage diseases, and rare diseases.

At least one Key Informant group conference call will be scheduled. The Key Informants will provide general guidance on the literature review, for example, years to include in the search and potential clinical outcomes. Because this technical brief involves six distinct diseases, the content experts may have additional disease-specific information to contribute. As a follow-up to the group conference call, the Key Informants will be interviewed individually by telephone, using a semi-structured interview outline which will provide the content experts the opportunity to share their experiences with patients with lysosomal storage disorders, their experience with ERT, and their opinions on unresolved or controversial issues relating to ERT.

One call with the patient advocates is planned. Because of the nature of lysosomal storage diseases, patients are predominantly children, so one adult patient and one parent of a child patient will be consulted. The patient and the parent will be asked about their experiences with the disorder prior to ERT and subsequent to ERT. They will be asked

to describe symptoms, outcomes, and factors involved in the decision to begin treatment with ERT.

B. Grey Literature search

Internet searches will be conducted in the United States Food and Drug Administration website concerning the 6 ERT treatments. Information will be used in answering Guiding Questions 1, 2, and 4.

The ERT manufacturers' websites will be searched to inform Guiding Questions 1 and 2:

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

Registries and patient advocate websites for each of the 6 LSDs will be searched.

Examples include:

http://www.marrow.org/PATIENT/Undrstnd_Disease_Treat/Lrn_about_Disease/Metabolic_Storage/Hurler_and_Tx/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/>, and <http://www.pompe.com/en/healthcare-professionals/pompe-registry.aspx>

Current trials involving ERT will be identified by searching clinicaltrials.gov.

C. Published Literature search

A scan of published medical literature will be conducted to address Guiding Question 3. English language searches will be performed in MEDLINE, Embase, the Cochrane Database, and the Health Technology Assessment Database. The search strategies were executed September 16, 2011, as follow.

Search 1 -

"Mucopolysaccharidosis I"[Mesh] OR ("mucopolysaccharidosis" AND "type 1") OR
"mucopolysaccharidosis I" OR "mucopolysaccharidosis-I" OR "MPS I" OR "Hurler
disease" OR "hurler syndrome"

AND

laronidase OR aldurazyme

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AND

English language, humans

results in PubMed = 36

29 additional studies identified using the search in EMBASE = 15 appeared to be unique and possibly relevant

Cochrane search found 4 trials – all are in the database.

Search 2 –

"Mucopolysaccharidosis II"[Mesh] OR (mucopolysaccharidosis AND "type II") OR "mucopolysaccharidosis II" OR "mucopolysaccharidosis-II" OR "MPS II" OR "Hunter disease" OR "hunter syndrome"

AND

"idursulfase" [Supplementary Concept] OR idursulfase OR elaprase

AND

English language, humans

Results in PubMed = 34

67 additional studies identified using the search in EMBASE = 3 appeared to be unique and possibly relevant

Cochrane search found 1 protocol and 2 trials that were unique and added to the database.

Search 3 –

"Mucopolysaccharidosis VI"[Mesh] OR (mucopolysaccharidosis AND "type VI") OR "mucopolysaccharidosis VI" OR "mucopolysaccharidosis-VI" OR "MPS VI" OR "maroteaux-lamy syndrome"

AND

"galsulfase" [Supplementary Concept] OR galsulfase OR naglazyme

AND

English language, humans

Results in PubMed = 21

24 additional studies identified using the search in EMBASE = 6 appeared to be unique and possibly relevant

Cochrane search found 1 new technology assessment which was added. Everything else was already there.

Search 4 –

"Fabry Disease"[Mesh] OR "fabry disease" OR "alpha-Galactosidase A Deficiency"

AND

"agalsidase beta" [Supplementary Concept] OR "agalsidase beta" OR fabrazyme

AND

English language, humans

Results in PubMed = 132

130 studies identified using the search in EMBASE = 13 appeared to be unique and possibly relevant

Cochrane search found 2 additional trials which were added.

Search 5 -

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"Gaucher Disease"[Mesh] OR "gaucher disease" OR "gaucher's disease"
AND
(("alglucerase" [Supplementary Concept]) OR "imiglucerase" [Supplementary Concept])
OR "Velaglucerase alfa, human" [Supplementary Concept] OR alglucerase OR ceredase
OR imiglucerase OR cerezyme OR velaglucerase OR "miglustat" [Supplementary
Concept] OR miglustat OR zavesca
AND
("type 1" OR "type I") OR various study types (RCT, meta-analysis, comparative study)
AND
English language, humans
Results in PubMed =222
65 clinical studies identified in EMBASE = 4 appeared to be unique and possibly
relevant
Cochrane search found 4 additional articles which were added.

Search 6 –

"Glycogen Storage Disease Type II"[Mesh] OR ("glycogen storage disease" AND ("type
II" OR "type 2")) OR "pompe disease" OR "pompe's disease"
AND
"GAA protein, human" [Supplementary Concept] OR "alglucosidase alfa" OR myozyme
AND
English language, humans
Results in PubMed =99
41 clinical studies identified in EMBASE = 8 appeared to be unique and possibly
relevant
Cochrane search found 2 trials – only 1 unique one – a meeting abstract – was added.

The DistillerSR Systematic Review Tool will be utilized to facilitate the screening and study selection process, as follows. Titles and abstracts will be screened to detect potential articles relevant to the topic. Full text articles of those marked as potentially relevant will be retrieved and screened for inclusion/exclusion in the review. Reports will be included if they describe clinical outcomes in patients with one of the 6 LSDs under consideration who received specific ERT for that disorder.

Due to the rarity of the diseases in this report, randomized clinical trials, simple before-after studies, case series and case reports will all be included. Reference lists of the included studies will also be reviewed to ensure that any relevant articles that may have been missed in the literature search, can then be added.

2. Data Organization and Presentation

A. Information Management

There are three main sources of information for this technical brief: published literature, grey literature, and key informants. Data from studies published in the medical literature will be abstracted and entered into the DistillerSR Systematic Review Tool. Data collected will include: study design, number of study subjects, severity of disease, ERT dosing and administration details, length of follow-up, pre-treatment physical and psychosocial measurements, post-treatment physical and psychosocial measurements, and adverse events. Information about clinical indications and dosing and administration recommendations, abstracted from guidelines and reviews in the medical literature and from pharmaceutical company websites, will be organized in a spreadsheet. Information from key informants, patient advocacy websites, and disease registries will be of a qualitative nature and will be managed in a Word document.

B. Data Presentation

There will be a graphical presentation of the level of evidence of ERT treatment for the 6 diseases, indicating the number of studies published and the number of patients included in the studies. The remaining data to be presented will be separated by disease. There will be summary tables of the published studies for each disease, which will include the following information: study design, patient population, pre-treatment physical and psychosocial measurements, post-treatment physical and psychosocial measurements, and adverse events. A narrative summary for each disease will incorporate the information gathered from the medical literature, the grey literature, and the key informants, and will 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.

IV. References

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2. Heese BA. Current strategies in the management of lysosomal storage diseases. *Semin Pediatr Neurol* 2008 Sep;15(3):119-26. PMID: 18708002
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4. Grabowski GA. Gaucher's disease. Enzyme therapy is not enough. *Lancet* 2001 Dec;358 Suppl:S29. PMID: 11784578

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7. Brady RO. Enzyme replacement for lysosomal diseases. *Annu Rev Med* 2006;57:283-96. PMID: 16409150
8. Brady RO, Schiffmann R. Enzyme-replacement therapy for metabolic storage disorders. *Lancet Neurol* 2004 Dec;3(12):752-6. PMID: 15556808
9. Bruni S, Loschi L, Incerti C, et al. Update on treatment of lysosomal storage diseases. *Acta Myol* 2007 Jul;26(1):87-92. PMID: 17915580

V. Definition of Terms

Abbreviations:

ERT	enzyme replacement therapy
GSD II	glycogen storage disease type II (Pompe disease)
IMD	inherited metabolic disorders
LSD	lysosomal storage disorders
MPS I	mucopolysaccharidosis I (Hurler disease)
MPS II	mucopolysaccharidosis II (Hunter disease)
MPS VI	mucopolysaccharidosis VI (Mariteaux-Lamy syndrome)

VI. Summary of Protocol Amendments

Protocol changes with the rationale for the change for ERT Technical Brief

Section	Protocol Deviation	Rationale
Methods	<p><i>Original study selection criteria in Protocol Methods:</i></p> <p>“Due to the rarity of the diseases in this report, randomized clinical trials, simple before-after studies, case</p>	<p>During the Topic Refinement phase of this project, we did not anticipate the presence of randomized clinical trials (RCTs) for any of the LSDs or ERT products under study. However, a comprehensive electronic search of</p>

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series and case reports will all be included. Reference lists of the included studies will also be reviewed to ensure that any relevant articles that may have been missed in the literature search, can then be added.”

Revised study selection in Technical Brief Methods:

“We searched the published medical literature in MEDLINE®, EMBASE®, the Cochrane Database, and the Health Technology Assessment Database to address Guiding Question 3. Based on input from the Key Informants, the initial 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, no longer marketed) received FDA marketing approval. The search was updated on April 24, 2012, while the draft was under peer review.

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 retrieved selected narrative or systematic review articles on ERT for the pertinent LSDs to provide background materials.

Preclinical studies, meeting abstracts, foreign-language articles, editorials, comments, and letters to the editor were excluded in the first-level title and abstract screen.

Reports were eligible for full-text screening if the abstract provided clinical outcomes in patients who received an FDA-approved ERT product; if an abstract wasn't available but the title was deemed

Medline, EMBASE, and the Cochrane Controlled Trials database showed that RCTs were available for all FDA-approved ERT products. There also were a number of prospective phase I and II clinical studies that complemented the RCTs. Given that RCTs comprise the best evidence in a hierarchy that takes into account risk of bias, and internal validity, we made a decision to compile the RCTs in the evidence map, supplementing them with prospective phase I and II studies that covered other clinical outcomes and patient subgroups. Given the existence of higher-level evidence, we did not include case series, case-control studies, or case reports in the evidence compilations presented in the body of the report.

However, because there was some reviewer concern about the comprehensiveness of our electronic and hand searches and study inclusion and exclusion, we included in an Appendix a resource bibliography that lists all the studies we identified as potentially relevant in our second-level screen of the literature search results.

potentially relevant, we retrieved the full text article for further examination. The search was limited to English-language reports based on evidence that suggests language restrictions do not change results of systematic review for conventional medical interventions.

In the second-level screen, full-text clinical studies were retrieved and screened for inclusion or exclusion in the literature compilations. We sought all randomized controlled trials (RCTs), in particular the pivotal trial or study submitted by the manufacturer for FDA approval for each ERT product. To alert readers and avoid oversampling, if more than one study was available with the same (or nearly same) study population, as in an extension study, we cross-indexed the trials in the tables. We also sought prospective phase I or II nonrandomized studies that included patient subgroups with specific disease manifestations not well represented in RCTs, or treatment protocols or settings that were not reported in RCTs. If higher-level studies (RCTs, prospective phase I and II) were not available, case series (single-arm studies), case-control studies, case reports, and prospective registry studies were eligible for the main evidence compilations.

We also sought registry reports to ascertain whether clinical outcomes reported in that type of publication were consistent with outcomes reported in clinical studies. Reference lists of the included studies and recent review articles were examined to identify other relevant articles. A resource bibliography that lists all the citations we examined in the second-level

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	literature screen is available in Appendix E. We did not assess study quality or the overall strength of the evidence”	
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VII. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will be published three months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

Table. Diseases with FDA-approved Enzyme Replacement Therapy*

Disease [estimated incidence]	Symptoms	FDA-Approved Product (approval date)
<p>MPS I (Hurler disease), 1/100,000 live births</p>	<p>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 3 groups:</p> <ul style="list-style-type: none"> - MPS IH, Hurler, is the most severe form with symptoms presenting within the first 12 mos 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 yrs of age. Symptoms may include growth deficiencies, deafness, coarse facial features, clouded corneas, umbilical hernia, heart disease, and moderate mental retardation. Life expectancy is late teens to early twenties. - MPS IS, Scheie, is the mildest form of the disease with symptoms presenting from 5-12 yrs 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. 	<p>Aldurazyme® (aronidase), Genzyme Corporation (April 2003)</p>
<p>MPS II (Hunter disease), 1/155,000 live births (1/34,000 live births in Israeli Jewish population)</p>	<p>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.</p> <ul style="list-style-type: none"> - The more severe form has CNS involvement with symptoms presenting by 2 yrs 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 yrs, with cause of death usually due to heart disease, from valvular, myocardial, and ischemic factors. 	<p>Elaprase® (idursulfase), Shire Human Genetic Therapies Inc (July 2006)</p>

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	<p>- 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 yrs.</p>	
<p>MPS VI (Maroteaux-Lamy syndrome), 1/340,000 live births</p>	<p>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 yrs to later adulthood, with cause of death usually from heart disease or airway obstruction.</p>	<p>NAGLAZYME® (galsulfase), BioMarin Pharmaceutical Inc (June 2005)</p>
<p>Fabry's disease, 1/40,000 live male births</p>	<p>Fabry's disease is an X-linked disorder with an onset of symptoms and severity of symptoms that vary widely among pts. 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.</p> <p>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.</p> <p>Life expectancy is 40 - 50 yrs, with cause of death usually due to a decline in kidney function or to cardiovascular disease.</p>	<p>Fabrazyme® (agalsidase beta), Genzyme Corporation (April 2003)</p>
<p>Gaucher Type I, overall 1/50,000 live births (1/500-1000 live births among Ashkenazi Jewish)</p>	<p>Gaucher disease type I is the most common lysosomal storage disease. The onset of symptoms is variable, from early childhood to late adulthood. Pts presenting in early childhood have a more severe course of the disease compared to those presenting later in life.</p> <p>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.</p>	<p>Ceredase® (alglucerase), Genzyme Corporation (April 1991) Cerezyme® (imiglucerase), Genzyme Corporation (May 1994) Velaglucerase® (velaglucerase alfa), Shire Human Genetic Therapies</p>

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	<p>Some developmental delays may occur as a consequence of the persistent clinical symptoms.</p> <p>Life expectancy varies widely, depending on the severity of symptoms, and can extend to near normal expectancy.</p>	<p>Inc (March 2010) Zavesca® (miglustat), Actelion Pharmaceuticals, FDA approved in Aug 2003 for adult patients only</p>
<p>Glycogen Storage Disease type II (Pompe disease), 1/40,000 live births</p>	<p>There are two forms of Pompe disease.</p> <p>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 yr, with cause of death usually from cardiorespiratory failure or respiratory infection.</p> <p>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 vary markedly among pts. Pts 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.</p>	<p>Myozyme® (alglucosidase alfa), Genzyme Corporation</p>

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