AETNA BETTER HEALTH®

Clinical Policy Bulletin: Enzyme-replacement Therapy for Lysosomal Storage Disorders

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Policy

I. Imiglucerase (Cerezyme), Miglustat (Zavesca), Taliglucerase alfa (Elelyso), and Velaglucerase Alfa (VPRIV)

A. Aetna considers eliglustat (Cerdelga), imiglucerase (Cerezyme), miglustat (Zavesca), taliglucerase alfa (Elelyso), and velaglucerase alfa (VPRIV) medically necessary for adult members with Type 1 Gaucher disease who meet both of the following criteria:

1. Member has any of the following signs and symptoms:
   a. Moderate to severe anemia (hemoglobin less than or equal to 11.5 g/dL (adult women) or 12.5 g/dL (adult men) or less than or equal to 1.0 g/dL or more below the lower limit of normal for age and sex); or
   b. Significant hepatomegaly (liver size 1.25 or more times normal (1,750 cc in adults)) or splenomegaly (spleen size 5 or more times normal (875 cc in adults)); or
   c. Skeletal disease beyond mild osteopenia and Erlenmeyer flask deformity; or
   d. Symptomatic disease, including abdominal or bone pain, fatigue, exertional limitation, weakness, or cachexia; or
   e. Thrombocytopenia (platelet count less than or equal to 120,000/mm3); and
2. For eliglustat (Cerdelga) only, member is a CYP2D6 extensive metabolizer (EM), intermediate metabolizer (IM), or poor metabolizer (PM) (According to the FDA approved labeling, CYP2D6 ultra-rapid metabolizers (UMs) may not achieve adequate concentrations of Cerdelga to achieve a therapeutic effect.)

B. Aetna considers **eliglustat**, imiglucerase, miglustat, taliglucerase alfa, and velaglucerase alfa medically necessary for children and adolescents less than 18 years of age who are diagnosed with Type 1 Gaucher disease.

C. Aetna considers **eliglustat**, imiglucerase, taliglucerase alpha and velaglucerase alpha (VPRIV) medically necessary for children and adults diagnosed with neuronopathic Type 3 Gaucher disease who meet medical necessity criteria in section A and have neurologic findings consistent with Type 3 Gaucher disease (encephalopathy, ophthalmoplegia, progressive myoclonic epilepsy, cerebellar ataxia, spasticity or dementia).

D. Aetna considers **eliglustat**, imiglucerase, miglustat, taliglucerase alfa, and velaglucerase alfa experimental and investigational for all other indications because of insufficient evidence in the peer-reviewed literature.

This policy is based, in part, on the recommendations of the International Collaborative Gaucher Group U.S. Regional Coordinators and the National Institutes of Health Technology Assessment Conference on Gaucher Disease.

See also Aetna Pharmacy Clinical Policy Bulletin: Gaucher Disease Agents.

**I. Aronidase (Aldurazyme)**

Aetna considers **aronidase** (Aldurazyme) medically necessary for members diagnosed with Hurler and Hurler-Scheie forms of mucopolysaccharidoses I (MPS I) and for members diagnosed with the Scheie form who have moderate to severe symptoms (see appendix).

Aetna considers **aronidase** experimental and investigational for all other indications including treatment of members with the Scheie form of MPS I who have mild symptoms, as the risks and benefits of treating mildly affected persons with the Scheie form have not been established.

**III. Agalsidase Beta (Fabrazyme)**

Aetna considers **agalsidase beta** (Fabrazyme) medically necessary for use in members diagnosed with Fabry disease.

Aetna considers **agalsidase beta** experimental and investigational for all other indications because its effectiveness for indications other than the one listed has not been established.

**IV. Galsulfase (Naglazyme)**
Aetna considers galsulfase (Naglazyme) medically necessary for the treatment of members with mucopolysaccharidosis VI (MPS VI).

Aetna considers galsulfase experimental and investigational for all other indications because its effectiveness for indications other than the one listed has not been established.

V. Alglucosidase Alfa (Myozyme)

Aetna considers alglucosidase alfa (Myozyme) medically necessary for the treatment of members with infantile-onset Pompe disease.

Aetna considers alglucosidase alpha experimental and investigational for all other indications including treatment of persons with other forms of Pompe disease because according to the Food and Drug Administration (FDA), alglucosidase alpha has not been adequately studied in these other forms of Pompe disease to assure safety and efficacy.

VI. Alglucosidase Alfa (Lumizyme)

Aetna considers alglucosidase alfa (Lumizyme) medically necessary for the treatment of individuals with Pompe disease.

Aetna considers alglucosidase alfa experimental and investigational for all other indications because its effectiveness for indications other than the one listed has not been established.

VII. Idursulfase (Elaprase)

Aetna considers idursulfase (Elaprase) medically necessary for the treatment of members with Hunter syndrome (mucopolysaccharidosis II).

Aetna considers idursulfase experimental and investigational for all other indications because its effectiveness for indications other than the one listed has not been established.

VIII. Elsulfase Alfa (Vimizim)

Elsulfase alfa (Vimizim) is considered medically necessary for members with a documented clinical diagnosis of mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome). Based on clinical signs and symptoms of MPS IVA and documented reduced fibroblast or leukocyte N-acetylgalactosamine-6 sulfatase (GALNS) enzyme activity or genetic testing confirming diagnosis of MPS IVA.

Aetna considers elsulfase experimental and investigational for all other indications because its effectiveness for indications other than the one listed has not been established.
Background

Gaucher Disease

Currently, imiglucerase (Cerezyme), miglustat (Zavesca), taliglucerase alfa (Eleyso), and velaglucerase (VPRIV) are the treatments available for Type 1 (non-neuropathic) Gaucher disease.

Algglucerase (Ceredase) is the first-generation enzyme replacement therapy (ERT) product for Gaucher's disease marketed by Genzyme Corp. (Cambridge, MA) and imiglucerase is Genzyme's second-generation Gaucher disease product. Algglucerase has been withdrawn from the market. They have not been shown to reverse or ameliorate neurological symptoms associated with Type 2 (acute neuronopathic) Gaucher disease. Algglucerase and imiglucerase have also not been shown to improve health outcomes in patients with Type 1 Gaucher disease without signs or symptoms of disease.

Enzyme replacement therapy also is used for individuals known to be at-risk for neuronopathic type 3 disease due to genotype or family history who present before the onset of neurologic symptoms. ERT may stabilize the neurologic progression in some of these patients or be effective only on the somatic signs and symptoms.

At this time, no effective minimum dosage has been established for algglucerase or imiglucerase. These drugs are administered no more than 3 times per week. The patient's response is reassessed at least every 3 months, with the intent of adjusting the frequency and size of doses.

Algglucerase and imiglucerase are administered by intravenous infusion over a period of 1 to 2 hours. Dosage should be individualized for each patient. According to the United States (U.S.) Food and Drug Administration (FDA) approved labeling for imiglucerase (Cerezyme), initial dosages range from 2.5 units per kilogram of body weight 3 times a week up to as much as 60 units/kg administered once every 2 weeks. Disease severity may dictate that treatment be initiated at a relatively high dose or relatively frequent administration. Dosage adjustments should be made on an individual basis and may increase or decrease, based on achievement of therapeutic goals as assessed by routine comprehensive evaluations of the patient's clinical manifestations. Doses as low as 1 unit/kg monthly may be adequate for some patients. The dose for which the most data are available is 60 units/kg every 2 weeks.

Disease severity may dictate that the drug be initiated with relatively high doses or relatively frequent administration. After patient response is well-established, a reduction in dosage may be attempted for maintenance therapy. Progressive reductions can be made at intervals of 3 to 6 months while carefully monitoring response parameters.

The International Collaborative Gaucher Group (ICGG) U.S. Regional Coordinators recommend that all children with Gaucher disease be treated with ERT. Children with Gaucher disease are at high-risk for irreversible, morbid complications. The diagnosis of Gaucher disease in the 1st and 2nd decades of life is indicative of a rapidly progressive course. Early intervention is necessary for these children, during the time when the skeleton is immature, to enable them to attain their peak skeletal mass by early adulthood.

Velaglucerase alfa (gene-activated human glucocerebrosidase) is an ERT for the treatment of Gaucher disease. It is produced in a human cell line using gene-activation technology and has an identical amino acid sequence to the naturally occurring human enzyme. In contrast to imiglucerase, velaglucerase alfa contains the native human
enzyme sequence. Kinetic parameters (K(m) and V(max)) of velaglucerase alfa and imiglucerase, as well as their specific activities, are similar. However, analysis of glycosylation patterns shows that velaglucerase alfa displays distinctly different structures from imiglucerase. The predominant glycan on velaglucerase alfa is a high-mannose type, with 9 mannose units, while imiglucerase contains a chitobiose tri-mannosyl core glycan with fucosylation. These differences in glycosylation affect cellular internalization; the rate of velaglucerase alfa internalization into human macrophages is at least 2-fold greater than that of imiglucerase (Brumstein et al, 2010).

Shire Human Genetic Therapies, Inc. (2010) presented positive results from its first phase III study of velaglucerase alfa for the treatment of Type 1 Gaucher disease. This trial was a 12-month, randomized, double-blind, parallel-group global study in 25 treatment-naive patients aged 2 years and older that evaluated velaglucerase alfa at dosages of 45 U/kg and 60 U/kg. The study’s primary endpoint, mean hemoglobin concentration changes from baseline, was represented by a statistically significant increase of 23.3 % (+2.43 +/- 0.32 g/dL, p < 0.0001) at 12 months in the 60 U/kg group. Secondary endpoints for both doses were changes in platelet counts, changes in organ volumes, changes in surrogate markers of Gaucher disease, and for the 45 U/kg dose only, change in hemoglobin concentrations from baseline.

In January 2010, the FDA approved velaglucerase alfa for injection (VPRIV) to treat children and adults with Type I Gaucher disease. The approval was based on a priority review of data from 3 clinical studies of 82 patients aged 4 years and older, some of whom switched from imiglucerase therapy. The recommended velaglucerase regimen is 60 IU/kg administered every other week as a 1-hour intravenous infusion. The most common adverse reactions to VPRIV are allergic reactions. Other observed adverse reactions with VPRIV are headache, dizziness, abdominal pain, back pain, joint pain, nausea, fatigue/weakness, fever, and prolongation of activated partial thromboplastin time. Pediatric patients were more likely than adults (greater than 10 % difference) to experience rash, upper respiratory tract infection, prolonged partial thromboplastin time, and pyrexia.

Most recently, miglustat (Zavesca) is an oral ERT that has been approved by the FDA for the treatment of adult patients with mild-to-moderate Type 1 Gaucher disease for whom infusion/injection ERT is not a therapeutic option (e.g., due to constraints such as allergy, hypersensitivity, or poor venous access).

In clinical studies, the most common adverse events due to miglustat included weight loss, diarrhea, and trembling in the hand (tremor). The most common serious adverse reaction was tingling or numbness in the hands or feet with or without pain (peripheral neuropathy). The labeling for Zavesca states that patients should undergo neurological examination at the start of treatment and every 6 months thereafter, and that Zavesca should be reassessed in patients who develop symptoms of peripheral neuropathy.

According to the labeling, the recommended dose for the treatment of adult patients with Type 1 Gaucher disease is one 100-mg capsule administered orally 3 times a day at regular intervals.

Talgilucerase alfa is a plant cell-derived recombinant human β-glucocerebrosidase for Gaucher disease. Zimran et al (2011) performed a phase III, double-blind, randomized, parallel-group, comparison-dose (30 versus 60 U/kg body weight/infusion) multi-national clinical trial. A 9-month, 20-infusion trial used inclusion/exclusion criteria in treatment-naive adult patients with splenomegaly and thrombocytopenia. Safety end points were drug-related adverse events: Ab formation and hypersensitivity reactions. Primary efficacy end point was reduction in splenic volume measured by magnetic resonance imaging. Secondary end points were: changes in hemoglobin, hepatic volume, and platelet counts.
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Exploratory parameters included biomarkers and bone imaging. A total of 29 (11 centers) completed the protocol. There were no serious adverse events; drug-related adverse events were mild/moderate and transient. Two patients (6%) developed non-neutralizing IgG Abs; 2 other patients (6%) developed hypersensitivity reactions. Statistically significant spleen reduction was achieved at 9 months: 26.9% (95% confidence interval [CI]: -31.9 to -21.8) in the 30-unit dose group and 38.0% (95% CI: -43.4 to -32.8) in the 60-unit dose group (both p < 0.0001); and in all secondary efficacy end point measures, except platelet counts at the lower dose. These results support safety and effectiveness of taliglucerase alfa for Gaucher disease.

On May 1, 2012, the FDA approved taliglucerase alfa (Elelyso) for long-term enzyme replacement therapy to treat Type 1 Gaucher disease. According to the FDA, due to the small number of affected patients, the effectiveness of Elelyso was evaluated in a total of 56 patients with Type 1 Gaucher disease enrolled in 2 clinical trials. Many of these patients continued treatment on a longer-term extension study. In a multi-center, double-blind, parallel-dose trial, the effectiveness of Elelyso for use as an initial therapy was evaluated in 31 adult patients who had not previously received enzyme replacement therapy. Patients were randomly selected to receive Elelyso at a dose of either 30 or 60 units/kg. At both doses, Elelyso was effective in reducing spleen volume, the study’s primary endpoint, from baseline by an average of 29% in patients receiving the 30 units/kg dose and by an average of 40% in patients receiving the 60 units/kg dose after 9 months of treatment. Improvements in liver volume, blood platelet counts, and red blood cell (hemoglobin) levels also were observed.

The effectiveness of Elelyso was evaluated in another study of 25 patients with Type 1 Gaucher disease who were switched from imiglucerase. In this multi-center, open-label, single-arm trial, patients who had been receiving treatment with imiglucerase for at least 2 years were switched to Elelyso infusions every other week at the same dose of imiglucerase. Results showed Elelyso was effective in maintaining spleen and liver volumes, blood platelet counts, and hemoglobin levels over a 9-month evaluation period.

The most common side effects associated with the use of Elelyso were infusion reactions and allergic reactions. Symptoms of infusion reactions include headache, chest pain or discomfort, weakness, fatigue, hives, skin redness, increased blood pressure, back pain, joint pain, and flushing. As with other intravenous protein products, anaphylaxis has been observed in some patients during Elelyso infusions. Other commonly observed side effects observed in greater than 10% of patients treated with Elelyso included arthralgia, back pain, extremity pain, headache, influenza, nasopharyngitis, upper respiratory tract infection, and urinary tract infections.

The U.S. Food and Drug Administration (FDA) approved eliglustrat (Cerdelga) capsules for certain adult Gaucher disease type 1 patients (Genzyme, 2014). Eliglustrat is a specific ceramide analogue inhibitor of the enzyme glucosylceramide synthase (IC50 = 10 ng/mL) with broad tissue distribution, which results in reduced production of glucosylceramide. Glucosylceramide is the substance that builds up in the cells and tissues of people with Gaucher disease.

The FDA approval was based on efficacy data from two positive Phase 3 studies for eliglustrat: one in patients new to therapy (Trial 1), and the other in patients switching from approved enzyme replacement therapies (Trial 2) (Genzyme, 2014). The filing also incorporated four years of efficacy data from the Cerdelga Phase 2 study.

In Trial 1, improvements were seen across the following endpoints after 9 months on eliglustrat: spleen size, platelet levels, hemoglobin levels, and liver volume (Genzyme, 2014). Patients continue to receive eliglustrat in the extension period, and the majority of patients have been on treatment for over eighteen months. Trial 2 met the pre-specified criteria for non-inferiority to an enzyme replacement therapy (imiglucerase), which was a composite endpoint of each of the following parameters: spleen volume, hemoglobin...
levels, platelet counts, and liver volume. Patients continue to receive eliglustat in the extension period, and the majority of patients have been on treatment for over two years.

The most common adverse reactions (≥10%) are fatigue, headache, nausea, diarrhea, back pain, pain in extremities, and upper abdominal pain (Genzyme, 2014).

Eliglustat capsules are indicated for the long-term treatment of adults with Gaucher disease type 1 (GD1) who are CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test (Genzyme, 2014). Patients who are CYP2D6 ultra-rapid metabolizers (URMs) may not achieve adequate concentrations of CERDELGA to achieve a therapeutic effect. The labeling of Cerdelga states that a specific dose cannot be recommended for those patients whose CYP2D6 genotype cannot be determined (indeterminate metabolizers).

Eliglustat is contraindicated in the following patients due to the risk of significantly increased eliglustat plasma concentrations which may result in prolongation of the PR, QTc, and/or QRS cardiac intervals that could result in cardiac arrhythmias: EMs or IMs taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor and IMs or PMs taking a strong CYP3A inhibitor (Genzyme, 2014).

The labeling states that drugs that inhibit CYP2D6 and CYP3A may significantly increase the exposure to eliglustat; eliglustat dose adjustment may be needed, depending on metabolizer status (Genzyme, 2014). The recommended dosing for CYP2D6 EMs or IMs is 84 mg twice daily. The recommended dose for CYP2D6 PMs is 84 mg once daily.

Because eliglustat is predicted to cause increases in ECG intervals at substantially elevated plasma concentrations, use is not recommended in patients with pre-existing cardiac disease, long QT syndrome, or in combination with Class IA and Class III antiarrhythmic medications (Genzyme, 2014).

The labeling states that eliglustat should only be administered during pregnancy if the potential benefit justifies the potential risk; based on animal data, eliglustat may cause fetal harm (Genzyme, 2014). The labeling recommends discontinuing drug or nursing based on importance of drug to mother. Eliglustat is not recommended in patients with moderate to severe renal impairment or in patients with hepatic impairment.

Mucopolysaccharidosis I (MPS I)

The mucopolysaccharidoses (MPSs) are a group of inherited lysosomal storage disorders caused by the deficiency of specific enzymes that are required for the degradation of glycosaminoglycans (GAGs), or mucopolysaccharides. Mucopolysaccharidosis I disease (MPS I) is a progressive, autosomal recessive genetic disorder resulting from a defect in the gene for the lysosomal enzyme alpha-L-iduronidase. It is estimated that approximately 1,000 persons are afflicted with MPS I in the U.S. This enzyme deficiency results in an accumulation of the glycosaminoglycans dermatan sulfate and heparan sulfate, which are components of the extracellular matrix and connective tissues throughout the body. The inability to catabolize GAG results in its accumulation in the lysosome, resulting in cell, tissue, and organ dysfunction. Mucopolysaccharidosis I disease results in a variety of clinical manifestations, including umbilical and inguinal hernias, skeletal abnormalities, recurrent and persistent upper respiratory tract infections, coarse facial features, arthropathy, hydrocephalus, spinal root and peripheral nerve entrapment, obstructive airway disease, sleep apnea, hearing loss, hepatosplenomegaly, corneal clouding, glaucoma, retinal degeneration, optic trophy, cardiac valvular and ischemic myocardial damage. The diagnosis of MPS I is established by enzyme assay that measures alpha-L-iduronidase activity in leukocytes, plasma, or cultured skin fibroblasts. Enzyme activity is markedly deficient (less than 1 % normal) in affected patients. Prenatal diagnosis by
measurement of alpha-L-iduronidase activity in cultured amniocytes or chorionic villi is also possible.

Laronidase is administered to provide exogenous enzyme for uptake into the lysosomes in order to increase the catabolism of GAG. Enzyme replacement therapy with laronidase has been shown to provide clinically important benefits, such as improved pulmonary function and walking ability and reduction of excess carbohydrates stored in organs. In a randomized, placebo-controlled clinical study for the FDA's approval of laronidase, 45 MPS I patients were randomly assigned to laronidase or placebo. After 26 weeks, patients treated with laronidase showed statistically significant improvement in forced vital capacity (FVC) (median difference of 2 % (95 % CI: 0.4 to 7)) compared to placebo-treated patients. In addition, laronidase-treated patients showed a trend toward improvement in distance walked in 6 mins (median difference 39 meters (95 % CI: -2 to 79) compared to placebo-treated patients; however, this difference was not statistically significant. Liver size and urinary GAG levels decreased in patients treated with laronidase compared to patients treated with placebo.

All 45 patients received open-label laronidase for 36 weeks following the double-blind period. Maintenance of mean FVC and an additional increase in mean distance walked in 6 mins were observed compared to the start of the open-label period among patients who were initially randomized to and then continued to receive laronidase. Among patients who had been initially randomized to placebo, improvements from baseline in mean FVC and distance walked in 6 mins were observed compared to the start of the open-label period.

Laronidase is administered intravenously once-weekly. The recommended dosage for laronidase is 0.58 mg/kg. There is no published information on the effect on response rates of increased doses of laronidase beyond the FDA-recommended dosage. As a prerequisite for approval, the FDA has required the manufacturer to conduct post-marketing studies of different dosages and schedules of laronidase in clinical response. At this point, there is no evidence to support dosing laronidase beyond that recommended in the product labeling.

The most common adverse reactions associated with laronidase in clinical studies were upper respiratory tract infection, rash, and injection site reaction. The most common adverse reactions requiring intervention were infusion-related hypersensitivity reactions, including flushing, fever, headache, and rash.

Corrective surgery may be necessary for MPS I patients with joint contractures or foot and hand deformities. Corneal transplants may be required if vision problems become severe.

Grewal and colleagues (2005) described their initial experience with combined use of laronidase and hematopoietic stem cell transplantation in the treatment of patients with Hurler syndrome (n = 12). They concluded that in children with Hurler syndrome, laronidase and hematopoietic stem cell transplantation is feasible and well-tolerated.

Development of antibodies against exogenous enzyme does not appear to correlate with infusion reactions or response to laronidase. A prospective study is needed to ascertain the effect of concomitant ERT on transplant outcomes.

**Fabry Disease**

Fabry disease is a progressive, X-linked genetic disorder resulting from a defect in the gene for the lysosomal enzyme, alpha-GAL. This enzyme deficiency results in an
accumulation of globotriosylceramide (GL-3) and other lipids in tissues throughout the body. The inability to catabolize GL-3 can lead to renal failure, cardiomyopathy, and cerebrovascular accidents. The estimated incidence of Fabry disease is 1 in 40,000 males. Diagnosis of Fabry disease is confirmed by low or absent alpha-galactosidase activity in plasma or serum, leukocytes, tears, biopsied tissues, or cultured skin fibroblasts.

Agalsidase beta reduces GL-3 deposition from the interstitial endothelium of the kidney and certain other cell types. The reduction of GL-3 inclusions suggests that agalsidase beta may ameliorate disease expression of Fabry disease; however, the FDA-approved labeling notes that the relationship of GL-3 inclusion reduction to specific clinical manifestations of Fabry disease has not been established.

Agalsidase beta is administered by intravenous infusion every 2 weeks. The recommended dosage for agalsidase beta is 1.0 mg/kg. In clinical studies of agalsidase beta submitted to the FDA for approval, 58 Fabry patients were randomly assigned to 5 months treatment with either agalsidase beta or placebo. The primary efficacy endpoint of GL-3 inclusions in renal interstitial capillary endothelial cells, was assessed by light microscopy and was graded on an inclusion severity score ranging from 0 (normal or near normal) to 3 (severe inclusions). A GL-3 inclusion score of 0 was achieved by 20 of 29 (69%) patients treated with agalsidase beta compared to 0 of 29 patients treated with placebo (p < 0.001). Similar reductions in GL-3 inclusions were observed in the capillary endothelium of the heart and skin. However, during this 5-month study, no differences between groups in symptoms or renal function were observed.

The most serious and most common adverse reactions reported with agalsidase beta are infusion-associated reactions. Thus, the manufacturer recommends that patients be given antipyretics prior to infusion.

**Mucopolysaccharidosis VI**

Mucopolysaccharidosis VI (MPS VI), also known as Maroteaux-Lamy syndrome, is a debilitating, life-threatening genetic disease caused by a deficiency of the enzyme N-acetylgalactosamine 4-sulfatase. This deficiency results in the accumulation of glycosaminoglycans in the lysosomes, giving rise to progressive cellular, tissue and organ system dysfunction. An estimated 1,100 persons in the developed world have MPS VI. The majority of patients with MPS VI die from disease-related complications between childhood and early adulthood.

Harmatz and associates (2004) assessed the safety and effectiveness of weekly treatment with human recombinant N-acetylgalactosamine 4-sulfatase (rhASB) in humans with MPS VI. Patients were randomized to weekly infusions of either high (1.0 mg/kg) or low (0.2 mg/kg) doses of rhASB. Six patients (3 males, 3 females; aged 7 to 16 years) completed at least 24 weeks of treatment, 5 of this group have completed at least 48 weeks. No drug-related serious side effects, significant laboratory abnormalities, or allergic reactions were observed in the study. The high-dose group experienced a more rapid and larger relative reduction in urinary glycosaminoglycan that was sustained through week 48. Improvements in the 6-min walk test were observed in all patients with dramatic gains in those walking less than 100 meters at baseline. Shoulder range of motion improved in all patients at week 48 and joint pain improved in patients with significant pain at baseline. The authors concluded that rhASB treatment was well-tolerated and reduced lysosomal storage as indexed by a dose-dependent reduction in urinary glycosaminoglycan. Clinical responses were present in all patients, but the largest gains occurred in patients with advanced disease receiving high-dose rhASB.
On June 1, 2005, galsulfase (Naglazyme, BioMarin Pharmaceutical Inc., Novato, CA) was granted orphan drug status by the FDA for the treatment of MPS VI. Galsulfase has been reported to improve endurance as shown by the 12-min walk test as well as the 3-min stair climb. It reduces the urinary excretion of glycosaminoglycans, an indication of enzymatic bioactivity, in patients with MPS VI.

**Pompe Disease**

Infantile Pompe disease (IPD), also known as infantile acid maltase deficiency and type 2 glycogen storage disease, is an autosomal recessive muscle-wasting disorder due to a deficiency of the lysosomal enzyme acid alpha-glucosidase. The deficiency results in accumulation of glycogen in lysosomes and is characterized by progressive cardiomyopathy, skeletal muscle weakness and respiratory insufficiency leading to death in early infancy. Pompe disease is estimated to occur in about 1 in 40,000 live births.

On April 28, 2006, the FDA approved alglucosidase alfa, rhGAA (Myozyme), the first treatment for IPD. Alglucosidase alfa had been granted FDA orphan drug status and was approved under a priority review.

Alglucosidase alfa (Genzyme Corp, Cambridge, MA) is administered by intravenous infusion every 2 weeks. The recommended dosage is 20 mg/kg administered over approximately 4 hours. The safety and efficacy of alglucosidase alfa were assessed in 2 separate clinical trials in patients (n = 39) with infantile-onset Pompe disease ranging in age from 1 month to 3.5 years at the time of the first infusion. Patient survival without needing invasive ventilatory support was substantially greater in the alglucosidase alfa-treated infants than would be expected considering the high mortality rate of untreated patients of similar age and disease severity. According to the FDA, the drug's safety and effectiveness in other forms of Pompe disease have not been adequately studied.

A clinical study of the efficacy of alglucosidase alpha in persons with late-onset Pompe disease found statistically significant but modest effects (van der Ploeg et al, 2010). A total of 90 patients who were 8 years of age or older, ambulatory, and free of invasive ventilation were randomly assigned to receive bi-weekly intravenous alglucosidase alfa (20 mg/kg) or placebo for 78 weeks at 8 centers in the U.S. and Europe. The 2 primary end points were distance walked during a 6-min walk test and percentage of predicted forced vital capacity (FVC). At 78 weeks, the estimated mean changes from baseline in the primary end points favored alglucosidase alfa (an increase of 28.1 +/- 13.1 meters on the 6-min walk test and an absolute increase of 3.4 +/- 1.2 percentage points in FVC; p = 0.03 and p = 0.006, respectively). The authors concluded that their data indicated that alglucosidase alfa treatment, as compared with placebo, had a positive, if modest, effect on walking distance and pulmonary function in patients with late-onset Pompe's disease and may stabilize proximal limb and respiratory muscle strength. The authors noted that the study had a number of limitations. They noted that, although 90 patients is a large population for a clinical trial designed to study an orphan disease, the number is relatively small when the goal is to judge the progression of a clinically heterogeneous disease.

Before the start of this trial, no longitudinal data were available on changes in the 6-min walk test over time in patients with untreated Pompe's disease, and the mean decline in the distance walked was minimal in the patients in this study who received placebo.

"Longer follow-up will be needed to confirm our results, given the variable presentation and rate of deterioration among the patients in our study and the possible effect of the degree of muscle destruction at baseline on their response to treatment" (van der Ploeg et al, 2010).
In this study, similar proportions of patients in the 2 groups had adverse events, serious adverse events, and infusion-associated reactions; events that occurred only in patients who received the active study drug included anaphylactic reactions and infusion-associated reactions of urticaria, flushing, hyperhidrosis, chest discomfort, vomiting, and increased blood pressure (each of which occurred in 5 to 8% of the patients) (van der Ploeg et al, 2010). The most serious adverse reactions reported with alglucosidase alfa were heart and lung failure and allergic shock. Most common reactions included pneumonia, respiratory failure and distress, infections, and fever. A black box warning is included in the Myozyme label to warn about the possibility of life-threatening allergic reactions.

Late-onset glycogen storage disease type 2 (GSD2)/Pompe disease is a progressive multi-system disease evoked by a deficiency of lysosomal acid alpha-glucosidase (GAA) activity. It is characterized by respiratory and skeletal muscle weakness and atrophy, resulting in functional disability and reduced life span. Since 2006, alglucosidase alfa has been licensed as a treatment in all types of GSD2/Pompe disease. Srothotte et al (2010) presented an open-label, investigator-initiated observational study of alglucosidase alfa ERT in 44 late-onset GSD2 patients with various stages of disease severity. Alglucosidase alfa was given intravenously at the standard dose of 20 mg/kg every other week. Assessments included serial arm function tests (AFT), Walton Gardner Medwin scale (WGMS), timed 10-m walk tests, 4-stair climb tests, modified Gowers' maneuvers, 6-min walk tests, MRC sum score, FVC, creatine kinase (CK) levels and SF-36 self-reporting questionnaires. All tests were performed at baseline and every 3 months for 12 months of ERT. These researchers found significant changes from baseline in the modified Gowers' test, the CK levels and the 6-min walk test (341 +/- 149.49 m, median 342.25 m at baseline; 393 +/- 156.98 m; median 411.50 m at end point; p = 0.026), while all other tests were unchanged. Enzyme replacement therapy over 12 months revealed minor allergic reactions in 10% of the patients. No serious adverse events occurred. None of the patients died or required de novo ventilation. The authors stated that the clinical outcome data imply stabilization of neuromuscular deficits over 1 year with mild functional improvement.

On March 25, 2010, the FDA approved alglucosidase alfa (Lumizyme) for patients aged 8 years and older with late-onset (non-infantile) Pompe disease. Lumizyme is believed to work by replacing the deficient GAA, thereby reducing the accumulated glycogen in heart and skeletal muscle cells. On August 1, 2014, the U.S. Food and Drug Administration (FDA) approved the supplement to expand the indication for Lumizyme to all Pompe patients. The FDA reviewed newly available information and determined that Lumizyme and Myozyme are chemically and biochemically comparable. Consequently, the safety and effectiveness of Lumizyme and Myozyme are expected to be comparable. In addition, a single-center clinical study of 18 infantile-onset Pompe disease patients, aged 0.2 to 5.8 months at the time of first infusion, provided further support that infantile-onset patients treated with Lumizyme will have a similar improvement in ventilator-free survival as those treated with Myozyme.

Currently, the only other treatment for Pompe disease available in the U.S. is Myozyme, which is also manufactured by Genzyme. Myozyme has been in short supply due to limited manufacturing capacity. The manufacturer reserved Myozyme to treat infants and children with Pompe disease because younger patients generally have a much more aggressive form of the disease. Some adult patients in the U.S. received Lumizyme under a temporary access program. The approval of Lumizyme will ensure that treatment is available for all U.S. adult Pompe patients in need of treatment. Lumizyme’s safety and effectiveness have not been evaluated in patients with infantile-onset Pompe disease or in patients aged 8 years and younger with late-onset disease. These patients should be treated with Myozyme, not Lumizyme.

http://qawww.aetna.com/cpb/medical/data/400_499/0442_draft.html
Cupler and colleagues (2012) proposed consensus-based treatment and management recommendations for late-onset Pompe disease. A systematic review of the literature by a panel of specialists with expertise in Pompe disease was undertaken. A multi-disciplinary team should be involved to properly treat the pulmonary, neuromuscular, orthopedic, and gastro-intestinal elements of late-onset Pompe disease. Pre-symptomatic patients with subtle objective signs of Pompe disease (and patients symptomatic at diagnosis) should begin treatment with ERT immediately; pre-symptomatic patients without symptoms or signs should be observed without use of ERT. After 1 year of ERT, patients’ condition should be re-evaluated to determine whether ERT should be continued.

Hunter Syndrome

Hunter syndrome (mucopolysaccharidosis II) is an X-linked, recessive, lysosomal storage disease that is caused by a defect of the iduronate-2-sulfatase gene, and consequently female patients are rare. It is diagnosed in approximately 1 out of 65,000 to 132,000 births. Hunter syndrome usually becomes apparent in children 1 to 3 years of age. Symptoms include growth delay, joint stiffness, and coarsening of facial features. In severe cases, patients experience neurological deficits, enlargement of the liver and spleen, cardiac as well as respiratory problems, and death.

On July 24, 2006, the FDA approved idursulfase (Elaprase) (Shire Human Genetic Therapies, Inc., Cambridge, MA) for the treatment of Hunter syndrome. Idursulfase was designated as an orphan drug, and was approved after a randomized, double-blind, placebo-controlled clinical trial of 96 patients showed that the treated subjects had an improved capacity to walk. At the end of the 53-week study, patients who received idursulfase infusions experienced on average a 38-yard greater increase in the distance walked in 6 mins compared to the patients on placebo. The most serious side effects reported during the trial were hypersensitivity reactions to idursulfase that could be life-threatening. They included respiratory distress, drop in blood pressure, and seizure. Other frequent, but less serious side effects included fever, headache, and joint pain. The recommended dosage regimen of idursulfase is 0.5 mg/kg administered every week as an intravenous infusion.

Muenzer et al (2012) stated that intravenous ERT with idursulfase for Hunter syndrome has not been demonstrated to and is not predicted to cross the blood-brain barrier. Nearly all published experience with ERT with idursulfase has therefore been in patients without cognitive impairment (attenuated phenotype). Little formal guidance is available on the issues surrounding ERT in cognitively impaired patients with the severe phenotype. An expert panel was therefore convened to provide guidance on these issues. The clinical experience of the panel with 66 patients suggested that somatic improvements (e.g., reduction in liver volume, increased mobility, and reduction in frequency of respiratory infections) may occur in most severe patients. Cognitive benefits have not been seen. It was agreed that, in general, severe patients are candidates for at least a 6- to 12-month trial of ERT, excluding patients who are severely neurologically impaired, those in a vegetative state, or those who have a condition that may lead to near-term death. It is imperative that the treating physician discuss the goals of treatment, methods of assessment of response, and criteria for discontinuation of treatment with the family before ERT is initiated. The authors concluded that the decision to initiate ERT in severe Hunter syndrome should be made by the physician and parents; and must be based on realistic expectations of benefits and risks, with the understanding that ERT may be withdrawn in the absence of demonstrable benefits.

Mucopolysaccharidosis IV (Morquio Syndrome)
Mucopolysaccharidosis IV (MPS IV A and B), also known as Morquio syndrome, is an autosomal recessive mucopolysaccharide storage disease. There are two forms of Morquio syndrome, Type A and Type B, with similar clinical findings and autosomal inheritance. MPS IV A results from mutations in the gene encoding galactosamine-6-sulfatase (GALNS), located at 16q24.3. MPS IV B is due to beta-galactosidase deficiency. The clinical features result from accumulation of keratan sulfate and chondroitin-6-sulfate.

The enzymes deficient in Morquio syndrome (mucopolysaccharidosis type IV) are galactosamine-6-sulfatase (ie, N-acetyl-galactosamine-6-sulfate sulfatase) and β-galactosidase. The diagnosis is confirmed by direct enzymatic assay in leukocytes or fibroblasts.

Deficiency of the enzyme results in excessive lysosomal storage of keratan sulfate in many tissues and organs. This accumulation causes systemic skeletal dysplasia, short stature, and joint abnormalities, which limit mobility and endurance. Malformation of the thorax impairs respiratory function, and malformation of neck vertebrae and ligament weakness causes cervical spinal instability and, potentially, cord compression. Other symptoms may include hearing loss, corneal clouding, and heart valve disease. Morquio A syndrome is estimated to occur in 1 in 200,000 to 300,000 live births. Symptoms usually start between ages 1 and 3.

The U.S. Food and Drug Administration (FDA) has approved elosulfase alfa (Vimizim) for persons with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome). The FDA approval of elosulfase was based on a randomized controlled clinical trial and an uncontrolled extension study.

A 24-week, randomized, double-blind, placebo-controlled clinical trial of elosulfase alfa was conducted in 176 patients with MPS IVA, ages 5 to 57 years old. Patients were randomized to three treatment groups: elosulfase alfa 2 mg/kg once per week (n=58), elosulfase alfa 2 mg/kg once every other week (n=59), or placebo (n=59). All patients were treated with antihistamines prior to each infusion. The primary endpoint was the change from baseline in the distance walked in six minutes (six minute walk test, 6-MWT) at Week 24. The other endpoints included changes from baseline in the rate of stair climbing in three minutes (three-minute stair climb test, 3-MSCT) and changes from baseline in urine keratan sulfate (KS) levels at Week 24. The treatment effect in the distance walked in 6 minutes, compared to placebo, was 22.5 m (95% CI, 4.0, 40.9; p = 0.0174) in patients who received elosulfase 2 mg/kg once per week. There was no difference in the rate of stair climbing between patients who received elosulfase 2 mg/kg once per week and those who received placebo. Patients who received elosulfase 2 mg/kg once every other week performed similarly in the 6-MWT and 3-MSCT as those who received placebo. The reduction in urinary KS levels from baseline, a measure of pharmacodynamic effect, was greater in the elosulfase treatment groups compared to placebo. The FDA labeling states that the relationship between urinary KS and other measures of clinical response has not been established.

Patients who participated in the placebo-controlled trial were eligible to continue treatment in an open-label extension trial. One hundred seventy-three of 176 patients enrolled in the extension trial in which patients received elosulfase 2 mg/kg once per week (n=86) or elosulfase 2 mg/kg once every other week (n=87). In patients who continued to receive elosulfase 2 mg/kg once per week for another 48 weeks (for a total of 72-week exposure), walking ability showed no further improvement beyond the first 24 weeks of treatment in the placebo-controlled trial.
The most common side effects in patients treated with elosulfase alfa during clinical trials included fever, vomiting, headache, nausea, abdominal pain, chills and fatigue. The FDA approved labeling states that the safety and effectiveness of elosulfase alfa have not been established in pediatric patients less than 5 years of age. Elosulfase alfa was approved with a boxed warning to include the risk of anaphylaxis. During clinical trials, life-threatening anaphylactic reactions occurred in some patients during Vimizim infusions.

The recommended dose of elosulfase alfa is 2 mg per kg given intravenously over a minimum range of 3.5 to 4.5 hours, based on infusion volume, once every week.

Appendix

Table 1: Spectrum of mucopolysaccharidosis I (MPS I).

<table>
<thead>
<tr>
<th>Hurler</th>
<th>Hurler-Scheie</th>
<th>Scheie</th>
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</thead>
<tbody>
<tr>
<td>Severe developmental delay</td>
<td>Little or no intellectual defect</td>
<td>Normal intelligence</td>
</tr>
<tr>
<td>More progressive Severe respiratory disease</td>
<td>Respiratory disease</td>
<td>Less progressive physical problems</td>
</tr>
<tr>
<td>Obstructive airway disease</td>
<td>Obstructive airway disease</td>
<td>Corneal clouding</td>
</tr>
<tr>
<td>Death before age 10 years</td>
<td>Cardiovascular disease</td>
<td>Joint stiffness</td>
</tr>
<tr>
<td></td>
<td>Joint stiffness/contractures</td>
<td>Valvular heart disease</td>
</tr>
<tr>
<td></td>
<td>Skeletal abnormalities</td>
<td>Death in later decades</td>
</tr>
<tr>
<td></td>
<td>Decreased visual acuity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Death in teens and 20's</td>
<td></td>
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</tbody>
</table>
CPT Codes / HCPCS Codes / ICD-9 Codes

Other CPT codes related to the CPB:

96360 - 96361 Intravenous infusion, hydration
96365 - 96368 Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug)
96379 Unlisted therapeutic, prophylactic, or diagnostic intravenous or intra-arterial injection or infusion

Other HCPCS codes related to the CPB:

S9357 Home infusion therapy, enzyme replacement intravenous therapy; (e.g., Imiglucerase); administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits codes separately), per diem

*Alglucerase (Ceredase), Imiglucerase (Cerezyme), Miglulstat (Zavesca) taliglucerase alfa (Elelyso) and Velaglucerase alfa (VPRIV) (there is no specific code for Miglulstat (Zavesca) or VPRIV):

HCPCS codes covered if selection criteria are met:

J1786 Injection, imiglucerase, 10 units
J3060 Injection, taliglucerase alfa, 10 units
J3385 Injection, velaglucerase alfa, 100 units

ICD-9 codes covered if selection criteria are met:

272.7 Lipidoses [Gaucher's disease]

Other ICD-9 codes related to the CPB:

280.0 - 285.9 Anemia
287.30 - 287.5 Primary, secondary, and unspecified thrombocytopenia
294.10 - 294.9 Dementia
334.2 Primary cerebellar degeneration
345.10 - 345.11 Generalized convulsive epilepsy [progressive myoclonic epilepsy]
348.30 - 348.39 Encephalopathy, not elsewhere classified
367.52 Total or complete internal ophthalmoplegia
571.8 Other chronic nonalcoholic liver disease
733.90 Disorder of bone and cartilage, unspecified
780.79 Other malaise and fatigue
781.0  Abnormal involuntary movements [spasticity]
789.00 - 789.09  Abdominal pain
789.1  Hepatomegaly
789.2  Splenomegaly
799.4  Cachexia

*Laronidase (Aldurazyme):*

**HCPCS codes covered if selection criteria are met:**

J1931  Injection, laronidase, 0.1 mg

**ICD-9 codes covered if selection criteria are met:**

277.5  Mucopolysaccharidosis [MPS I] [Hurler's, Hurler-Schele and Scheie’s syndrome] [with moderate to severe symptoms]

*Agalsidase Beta (Fabrazyme):*

**HCPCS codes covered if selection criteria are met:**

J0180  Injection, algalsidase beta, 1 mg

**ICD-9 codes covered if selection criteria are met:**

272.7  Lipidoses [Fabry disease]

*Galsulfase (Naglazyme):*

**HCPCS codes covered if selection criteria are met:**

J1458  Injection, galsulfase, 1 mg

**ICD-9 codes covered if selection criteria are met:**

277.5  Mucopolysaccharidosis [MPS VI]

*Alglucosidase Alfa (Myozyme):*

**HCPCS codes covered if selection criteria are met:**

J0220  Injection, alglucosidase alfa, 10 mg, not otherwise specified

**ICD-9 codes covered if selection criteria are met:**

271.0  Glycogenosis [Pompe disease, infantile onset only]

*Alglucosidase Alfa (Lumizyme):*

**HCPCS codes covered if selection criteria are met:**

J0221  INJECTION, ALGLUCOSIDASE ALFA, (LUMIZYME), 10 MG
ICD-9 codes covered if selection criteria are met:

271.0 Glycogenosis [Pompe disease, late-onset only]

Idursulfase (Elaprase):

HCPCS codes covered if selection criteria are met:

J1743 Injection, idursulfase, 1 mg

ICD-9 codes covered if selection criteria are met:

277.5 Mucopolysaccharidosis [MPS II] [Hunter's syndrome]

Elosulfase alfa (Vimizim):

No specific code

ICD-9 codes covered if selection criteria are met:

277.5 Mucopolysaccharidosis [IVA (MPS IVA; Morquio A syndrome)]

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