Lysosomal Storage Disorder Treatments

Number: 0442

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Least Cost Medically Necessary Brands
Elelyso (taliglucerase alfa), VPRIV (Velaglucerase Alfa), Zavesca (miglustat) brands of enzyme replacement therapy are more costly to Aetna than other brands of enzyme replacement therapy (“least cost brands of enzyme replacement therapy) used for Gaucher Disease. There is a lack of reliable evidence that Elelyso, VPRIV, and Zavesca are superior to the least cost brands of enzyme replacement therapy for this indication: Cerezyme (imiglucerase). Therefore, Aetna considers Elelyso, VPRIV, and Zavesca to be medically necessary only if the member has a contraindication, intolerance or ineffective response to Cerezyme (imiglucerase) for Gaucher Disease.

Policy

Note: PRECERTIFICATION REQUIRED
Precertification of enzyme replacement drugs is required of all Aetna participating providers and members in applicable plan designs. For precertification of these drugs, call (866) 752-7021, or fax (866) 267-3277.

**Note:** Site of Care Utilization Management Policy applies to enzyme replacement drugs (Aldurazyme, Cerezyme, Elaprase, Elelyso, Fabrazyme, Kanuma, Lumizyme, Mepsevii, Naglazyme, Vimizim, and Vpriv). For information on site of service for these drugs, see [Utilization Management Policy on Site of Care for Specialty Drug Infusions](http://www.aetna.com/products/rxnonmedicare/data/2018/ENDO/gaucher_disease.html).

I. Eliglustat (Cerdelga)

A. Aetna considers eliglustat (Cerdelga) medically necessary for treatment of Gaucher disease type 1 when all of the following criteria are met:

1. Diagnosis of Gaucher disease was confirmed by enzyme assay demonstrating a deficiency of beta-glucocerebrosidase (glucosidase) enzyme activity or by genetic testing; and
2. Member is a CYP2D6 extensive metabolizer, an intermediate metabolizer, or a poor metabolizer as detected by an FDA-cleared test.

**Note:** 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 continued therapy with eliglustat medically necessary for members with Type 1 Gaucher disease who are not experiencing an
inadequate response or any intolerable adverse
events from therapy

II. Imiglucerase (Cerezyme), Taliglucerase alfa (Elelyso),
and Velaglucerase alfa (VPRIV)

A. Aetna considers imiglucerase (Cerezyme),
taliglucerase alfa (Elelyso), and velaglucerase alfa
(VPRIV) medically necessary for treatment of
Gaucher disease type 1 when all of the following
criteria are met:

1. Diagnosis of Gaucher disease was confirmed by
   enzyme assay demonstrating a deficiency of beta-
   glucocerebrosidase (glucosidase) enzyme activity
   or by genetic testing.

B. Aetna considers imiglucerase (Cerezyme),
taliglucerase alfa (Elelyso), and velaglucerase alfa
(VPRIV) medically necessary for treatment of
Gaucher disease type 3 when all of the following
criteria are met:

1. Diagnosis of Gaucher disease was confirmed by
   enzyme assay demonstrating a deficiency of beta-
   glucocerebrosidase (glucosidase) enzyme activity
   or by genetic testing.

C. Aetna considers continued therapy with
   imiglucerase, taliglucerase alpha, and velaglucerase
   alpha medically necessary for members with Type
   1 or Type 3 Gaucher disease who are not
   experiencing an inadequate response or any
   intolerable adverse events from therapy.

III. Miglustat (Zavesca)
A. Aetna considers miglustat (Zavesca) medically necessary for treatment of Gaucher disease type 1 when all of the following criteria are met:

1. Diagnosis of Gaucher disease was confirmed by enzyme assay demonstrating a deficiency of beta-glucocerebrosidase (glucosidase) enzyme activity or by genetic testing; and
2. The member has a documented inadequate response or intolerable adverse events with enzyme replacement therapy.

B. Aetna considers continued therapy with miglustat medically necessary for members with Type 1 Gaucher disease who are not experiencing an inadequate response or any intolerable adverse events from therapy.

IV. Laronidase (Aldurazyme)

A. Aetna considers laronidase (Aldurazyme) medically necessary for members diagnosed with mucopolysacchararidoses I (MPS I) when the following criteria are met:

1. Diagnosis of MPS I was confirmed by enzyme assay demonstrating a deficiency of alpha-L-iduronidase enzyme activity or by genetic testing.
2. Member has the Hurler or Hurler-Scheie form of MPS I OR the member has the Scheie form (Scheie syndrome) with moderate to severe symptoms (e.g., normal intelligence, less progressive physical problems, corneal clouding, joint stiffness, valvular heart disease, death in later decades).
B. Aetna considers continued laronidase (Aldurazyme) therapy medically necessary for members with MPS I who are responding to therapy (e.g., improvement, stabilization, or slowing of disease progression for pulmonary function or walking capacity).

V. Agalsidase Beta (Fabrazyme)

A. Aetna considers agalsidase beta (Fabrazyme) medically necessary for members with Fabry disease when the diagnosis of Fabry disease was confirmed by enzyme assay demonstrating a deficiency of alpha-galactosidase enzyme activity or by genetic testing, or the member is a symptomatic obligate carrier.

B. Aetna considers use of agalsidase beta in combination with migalastat (Galafold) experimental and investigational.

C. Aetna considers continued therapy with agalsidase beta medically necessary for members with Fabry disease who are responding to therapy (e.g., reduction in plasma globotriaosylceramide [GL-3] or GL-3 inclusions).

D. 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.

VI. Galsulfase (Naglazyme)

A. Aetna considers galsulfase (Naglazyme) medically necessary for the treatment of members with mucopolysaccharidosis VI (MPS VI, Maroteaux-Lamy syndrome) when the diagnosis of MPS VI was confirmed by enzyme assay demonstrating a deficiency of N-acetylgalactosamine 4-sulfatase (arylsulfatase B) enzyme activity or by genetic testing.
B. Aetna considers continued treatment with galsulfase medically necessary for members with MPS VI who are responding to therapy (e.g., improvement, stabilization, or slowing of disease progression for 12-minute walk test [12-MWT] or 3-minute stair climb test [3-MSCT]).

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

VII. Alg glucosidase Alfa (Lumizyme)

A. Aetna considers alglucosidase alfa (Lumizyme, formerly Myozyme) medically necessary for the treatment of members with Pompe disease when the diagnosis of Pompe disease was confirmed by enzyme assay demonstrating a deficiency of acid alpha-glucosidase enzyme activity or by genetic testing.

B. Aetna considers continued treatment with alglucosidase alfa medically necessary for members with Pompe disease who are responding to therapy (e.g., improvement, stabilization, or slowing of disease progression for motor function, walking capacity, cardiorespiratory function, decrease in left ventricular mass index (LVMI), delay in death).

C. Aetna considers alglucosidase alfa experimental and investigational for all other indications.

VIII. Idursulfase (Elaprase)

A. Aetna considers idursulfase (Elaprase) medically necessary for the treatment of members with mucopolysaccharidosis II (MPS II, Hunter syndrome) when the diagnosis of MPS II was confirmed by
enzyme assay demonstrating a deficiency of iduronate 2-sulfatase enzyme activity or by genetic testing.

B. Aetna considers continued treatment with idursulfase medically necessary for members with MPS II who are responding to therapy (e.g., improvement, stabilization, or slowing of disease progression for 6-minute walk test [6-MWT], percent predicted FVC, spleen volume, or liver volume).

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

D. Aetna considers intrathecal idursulfase experimental and investigational for progressive cognitive impairment in individuals with MPS II because the effectiveness of this approach has not been established.

IX. Elosulfase Alfa (Vimizim)

A. Aetna considers elosulfase alfa (Vimizim) medically necessary for members with a documented clinical diagnosis of mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome) based on documented reduced leukocyte N-acetylgalactosamine-6 sulfatase (GALNS) enzyme activity or by genetic testing.

B. Aetna considers continued treatment with elosulfase alfa medically necessary for members with MPS IVA who are responding to therapy (e.g., improvement, stabilization, or slowing of disease progression for 6-minute walk test [6-MWT]).

C. Aetna considers elosulfase alfa experimental and investigational for all other indications because its effectiveness for indications other than the one listed has not been established.
X. Sebelipase Alfa (Kanuma)

A. Aetna considers sebelipase alfa (Kanuma) medically necessary for persons with a deficiency of lysosomal acid lipase (LAL) enzyme activity when the following criteria are met:

1. Deficiency of LAL deficiency is confirmed by an assay demonstrating a deficiency of lysosomal acid lipase (LAL) enzyme activity or by genetic testing; and
2. ALT greater than or equal to 1.5 times the upper limit of normal ULN (based on the age- and gender-specific normal ranges) on 2 consecutive ALT measurements obtained at least 1 week apart.

B. Aetna considers continued treatment with sebelipase alfa medically necessary for members with LAL deficiency who are responding to therapy (e.g., improvement, stabilization, or slowing of disease progression for weight-for-age z-score if exhibiting growth failure, LDL, HDL, triglycerides, or ALT).

C. Aetna considers sebelipase alfa experimental and investigational for all other indications.

XI. Cerliponase alfa (Brineura)

A. Aetna considers cerliponase alpha (Brineura) medically necessary for late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency and Jansky-Bielschowsky disease when all of the following criteria are met:
1. The diagnosis of CLN2 was confirmed by tripeptidyl peptidase 1 (TPP1) enzyme deficiency or by genetic testing; and
2. The member is 3 years of age or older; and
3. Cerliponase alfa will be administered by, or under the direction of a physician knowledgeable in intraventricular administration; and
4. Dosage of cerliponase alfa will not exceed 300 mg once every other week; and
5. The member does not have acute intraventricular access device-related complications (e.g., leakage, device failure, or device-related infection) or a ventriculoperitoneal shunt.

B. Aetna considers continued treatment with cerliponase alfa medically necessary for CLN2 when the following criteria are met:

1. Member has experienced a slowed loss of ambulation from baseline; and
2. Member does not have acute intraventricular access device-related complications (e.g., leakage, device failure, or device-related infection) or ventriculoperitoneal shunts.

C. Aetna considers cerliponase alfa experimental and investigational for all other indications.

XII. Vestronidase alfa-vjbk (Mepsevii)

A. Aetna considers vestronidase alfa-vjbk (Mepsevii) medically necessary for mucopolysaccharidosis type VII (MPS VII, Sly Syndrome) when the following criteria are met:
1. Diagnosis of MPS VII (MPS 7) based on deficiency of beta-glucuronidase enzyme activity or by genetic testing; and

2. Elevated urinary glycosaminoglycan (uGAG) excretion at a minimum of 2-fold over the mean normal for age at initiation.

B. Aetna considers continued treatment with vestronidase alfa-vjbk medically necessary for members with MPS VII who are responding to therapy (e.g., improvement, stabilization, or slowing of disease progression for motor function, pulmonary function, reduction in liver volume, reduction in spleen volume).

C. Aetna considers vestronidase alfa-vjbk experimental and investigational for all other indications.

XIII. Experimental treatments

Aetna considers eliglustat and miglustat experimental and investigational for Type 3 Gaucher disease because their effectiveness for this indication has not been established.

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.

Aetna considers concomitant use of eliglustat, imiglucerase, miglustat, taliglucerase alfa, and velaglucerase alfa experimental and investigational for Gaucher disease or for any other indication because the safety and efficacy of concomitant use has not been established.

Aetna considers the following interventions for the
treatment of mucopolysaccharidoses experimental and investigational because of insufficient evidence (not an all-inclusive list):

- Enzyme replacement therapy with fusion proteins
- Gene therapy
- Hematopoietic stem cell therapy
- Intrathecal enzyme replacement therapy
- Metallothioneins
- Pharmacological chaperone therapy (also known as enzyme-enhancement therapy)
- Substrate deprivation therapy
- Substrate reduction therapy.

Dosing Recommendations

Gaucher disease treatments

Cerdelga

Recommended Dosage Based on CYP2D6 Metabolizer Status

- EMs and IMs: 84 mg orally twice daily
- PMs: 84 mg orally once daily.

Dosage Adjustment in EMs and IMs With or Without Hepatic Impairment and Concomitant Use of CYP2D6 or CYP3A Inhibitors

Reduce dosage frequency of Cerdelga 84 mg to once daily in CYP2D6 EMs and IMs with or without hepatic impairment taking CYP2D6 or CYP3A inhibitors, as shown in Table 1 below:
**Table 1: Recommended dosage of Cerdelga 84 mg once daily based on CYP2D6 metabolizer, hepatic impairment status, and concomitant CYP inhibitors**

<table>
<thead>
<tr>
<th>CYP2D6 metabolizer status</th>
<th>Hepatic impairment status</th>
<th>Concomitant CYP inhibitor</th>
</tr>
</thead>
</table>
| EMs                       | Without hepatic impairment | ▪ Taking a strong or moderate CYP2D6 inhibitor  
                            |                           | ▪ Taking a strong or moderate CYP3A inhibitor |
|                           |                           |                          |
| Mild (Child-Pugh Class A) hepatic impairment | ▪ Taking a weak CYP2D6 inhibitor  
                            |                           | ▪ Taking a strong, moderate, or weak CYP3A inhibitor |
| IMs                       | Without hepatic impairment | Taking a strong or moderate CYP2D6 inhibitor |

**Cerezyme**

Cerezyme (imiglucerase for injection) is administered by intravenous infusion over 1 to 2 hours. Dosage should be individualized to each patient. Initial dosages range from 2.5

Proprietary
U/kg of body weight 3 times a week to 60 U/kg once every 2 weeks. 60 U/kg every 2 weeks is the dosage for which the most data are available. 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.

**Elelyso**

- Treatment-naïve: 60 units/kg administered every other week as a 60 to 120 minute intravenous infusion
- Patients switching from imiglucerase: Begin Elelyso at the same unit/kg dose as the patient's previous imiglucerase dose. Administer Elelyso every other week as a 60 to 120 minute intravenous infusion. Dosage adjustments can be based on achievement and maintenance of each patient's therapeutic goals.

**VPRIV**

Recommended Starting Dose in Adults and Pediatric Patients 4 Years of Age or Older:

- Patients Naïve to Enzyme Replacement Therapy: 60 Units/kg
- Patients being treated with stable imiglucerase dosages for Gaucher disease: Can switch to VPRIV at previous imiglucerase dose two weeks after last imiglucerase dose

**Zavesca**

- Recommended dosage is 100 mg administered orally three times a day at regular intervals
▪ May reduce dosage to 100 mg once or twice a day in some patients due to tremor or diarrhea
▪ Patients with renal impairment:

<table>
<thead>
<tr>
<th>Renal Impairment</th>
<th>Adjusted Creatinine Clearance (in mL/min/1.73 m²)</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>50-70</td>
<td>Start dose at 100 mg twice a day</td>
</tr>
<tr>
<td>Moderate</td>
<td>30-50</td>
<td>Start dose at 100 mg once a day</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt; 30</td>
<td>Use is not recommended</td>
</tr>
</tbody>
</table>

Other lysosomal storage disorder treatments

*Aldurazyme*

The recommended dosage is 0.58 mg/kg of body weight administered once weekly as an intravenous infusion.

*Brineura*

The recommended dosage is 300 mg administered once every other week as an intraventricular infusion followed by infusion of Intraventricular Electrolytes over approximately 4.5 hours.

*Elaprase*

The recommended dosage is 0.5 mg per kg of body weight administered once every week as an intravenous infusion.
**Fabrazyme**

The recommended dosage is 1 mg/kg body weight given every two weeks as an intravenous infusion.

**Kanuma**

- Patients with Rapidly Progressive LAL Deficiency Presenting within the First 6 Months of Life: The recommended starting dosage is 1 mg/kg as an intravenous infusion once weekly. For patients who do not achieve an optimal clinical response, increase to 3 mg/kg once weekly.
- Pediatric and Adult Patients with LAL Deficiency: The recommended dosage is 1 mg/kg as an intravenous infusion once every other week.

**Lumizyme**

The recommended dosage is 20 mg per kg body weight administered every 2 weeks as an intravenous infusion.

**Mepsevii**

The recommended dosage is 4 mg/kg administered every two weeks as an intravenous infusion.

**Naglazyme**

The recommended dosage is 1 mg per kg of body weight administered once weekly as an intravenous infusion.

**Vimizim**

The recommended dosage is 2 mg per kg body weight administered once every week as an intravenous infusion over a minimum of 3.5 to 4.5 hours, based on infusion volume.
Background

Gaucher Disease

Gaucher's disease, the most common of the lysosomal storage diseases, is caused by a deficiency of the enzyme glucocerebrosidase that leads to an accumulation of its substrate, glucocerebroside. Glucocerebroside can collect in the spleen, liver, kidneys, lungs, brain and bone marrow. Symptoms of the disease may include an enlarged spleen and liver, liver malfunction, skeletal disorders and bone lesions that may be painful, severe neurologic complications, swelling of lymph nodes and (occasionally) adjacent joints, distended abdomen, a brownish tint to the skin, anemia, low blood platelets, and yellow fatty deposits on the sclera. The disease shows autosomal recessive inheritance and therefore affects both males and females.

There are three common clinical subtypes. Type 1 (non-neuronopathic) disease is the most common form of the disease and may affect members in childhood or adulthood. Depending on disease onset and severity, these members may live well into adulthood.

Type 2 (acute neuronopathic) disease typically begins within six months of birth. In addition to the usual symptoms of the disease, there is extensive and progressive brain damage in this subtype; as such, affected children typically die by age two.

Type 3 (subacute or chronic neuronopathic) disease can begin in childhood or adulthood. Members with this subtype may live into their teen years and adulthood.

Type I Gaucher disease is the most common form and affects nearly 90% of diagnosed patients. Type I Gaucher disease does not involve nervous system organs, while type II and III
have nervous system involvement typically leading to mental retardation. 55-60% of type I Gaucher disease patients present before the age of 20.

There are 34 known mutations that cause Gaucher disease, but 4 genetic mutations account for 95% of cases in the Ashkenazi Jewish population and 50% of cases involving the general public. Gaucher disease occurs in about 1 out of every 75,000 births and the prevalence is equal among males and females. Amongst Ashkenazi Jew’, the prevalence is about 1 in 1,000 and 1 out of every 12 to 15 are carriers of the disease allele.

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

Alglucerase (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. Alglucerase has been withdrawn from the market.

Cerezyme (imiglucerase) is an analogue of the human enzyme ß-glucocerebrosidase, produced by recombinant DNA technology. ß-Glucocerebrosidase is a lysosomal glycoprotein enzyme which catalyzes the hydrolysis of the glycolipid glucocerebroside to glucose and ceramide.

Cerezyme (imiglucerase) is indicated for long-term enzyme replacement in pediatric and adult members 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.
They have not been shown to reverse or ameliorate neurological symptoms associated with Type 2 (acute neuronopathic) Gaucher disease. Alglucerase 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 alglucerase 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.

Alglucerase and imiglucerase are administered by intravenous infusion over a period of 1 to 2 hours. Dosage should be individualized for each patient, based on disease severity and patient response. Cerezyme (imiglucerase) is supplied as a sterile, non-pyrogenic, lyophilized product and is available as 200 Units per vial and 400 Units per vial. 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 two every weeks or as infrequently as every four 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.

Doses up to 240 units/kg IV, administered once every two weeks have been used without reports of toxicity, according to the manufacturer. A specific maximum dosage is not available, however, consensus guidelines state that doses > 60 units/kg IV once every two weeks are rarely necessary.

Although there are no known contraindications, Cerezyme (imiglucerase) should be used with caution in members with: a known hypersensitivity to imiglucerase; who are pregnant or breastfeeding; less than two years of age as data in this population is not available; or a high risk for pulmonary hypertension. Members with respiratory symptoms should be evaluated for the presence of pulmonary hypertension.

The use of Cerezyme (imiglucerase) should be directed by a qualified health care professional knowledgeable in the management of Gaucher's disease.

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) (Vpriv) for injection is an ERT for the treatment of Gaucher disease. Velaglucerase alfa is a hydrolytic lysosomal glucocerebroside-specific enzyme. Velaglucerase alfa catalyzes the hydrolysis of glucocerebroside, reducing the amount of accumulated glucocerebroside.

Velaglucerase 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 (Brumshtein 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.

Treatment with Vpriv should be approached with caution in patients who have exhibited symptoms of hypersensitivity to the active ingredient or excipients in the drug product or to other enzyme replacement therapy.

Hypersensitivity reactions, including anaphylaxis, occurred in clinical studies and postmarketing experience. Hypersensitivity reactions were the most commonly observed adverse reactions in patients treated with VPRIV in clinical studies. Patients were not routinely pre-medicated prior to infusion of Vpriv during clinical studies. The most commonly observed symptoms of hypersensitivity reactions were: headache, dizziness, hypotension, hypertension, nausea, fatigue(asthenia), and pyrexia/body temperature increased. Generally the reactions were mild and, in treatment-naïve patients, onset occurred mostly during the first 6 months of treatment and tended to occur less frequently with time.
Additional hypersensitivity reactions of chest discomfort, dyspnea, and pruritus have been reported in post-marketing experience.

As with any intravenous protein product, hypersensitivity reactions are possible, therefore appropriate medical support including personnel adequately trained in cardiopulmonary resuscitative measures and access to emergency measures should be readily available when VPRIV is administered. If anaphylactic or other acute reactions occur, immediately discontinue the infusion of VPRIV and initiate appropriate medical treatment. The management of hypersensitivity reactions should be based on the severity of the reaction, e.g., slowing the infusion rate, treatment with medications such as antihistamines, antipyretics and/or corticosteroids, and/or stopping and resuming treatment with increased infusion time. In cases where patients have exhibited symptoms of hypersensitivity to the active ingredient or excipients in the drug product or to other enzyme replacement therapy, pre-treatment with antihistamines and/or corticosteroids may prevent subsequent reactions.

Velaglucerase alfa for injection is available as Vpriv 400 Units single-use vials as a sterile powder for reconstitution. The recommended dose is 60 Units/kg administered every other week as a 60-minute intravenous infusion. Members currently being treated with imiglucerase for type 1 Gaucher disease may be switched to Vpriv. Patients previously treated on a stable dose of imiglucerase are recommended to begin treatment with Vpriv at that same dose when they switch from imiglucerase to Vpriv. Dosage adjustments can be made based on achievement and maintenance of each member’s therapeutic goals. Vpriv should be administered under the supervision of a healthcare professional.
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).

Zavesca (miglustat) is a competitive and reversible inhibitor of the enzyme glucosylceramide synthase, the initial enzyme responsible for the synthesis of glucosylceramide. Type 1 Gaucher patients are deficient in the enzyme glucocerebrosidase which is responsible for the degradation of glucosylceramide. Zavesca (miglustat) acts as a substrate reducer and allows the available glucocerebrosidase to act more efficiently.

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 re-assessed in patients who develop symptoms of peripheral neuropathy.

Approximately 85% of patients treated with Zavesca (miglustat) experienced diarrhea with or without weight loss. Incidence decreases over time and patients should avoid foods with high carbohydrate content. If diarrhea persists with usual interventions (e.g., diet modifications), the patient should be evaluated for underlying gastrointestinal disease.

Peripheral neuropathy has been reported and all patients should have neurological evaluations regularly.
Approximately 30% of patients treated with Zavesca (miglustat) reported tremors or exacerbation of existing tremor. Dose reduction may ameliorate tremors within days, but some patients will require discontinuation.

Pregnancy Category C: There are no adequate and well-controlled studies of Zavesca (miglustat) in pregnant women. Zavesca (miglustat) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Miglustat is available as Zavesca in 100 mg capsules. 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. Dosage may be reduced to 100 mg once or twice a day due to tremor or diarrhea.

Combination therapy with Cerezyme (imiglucerse) and Zavesca (miglustat) is not indicated.

Taliglucerase alfa (Elelyso) is a plant cell-derived recombinant human β-glucocerebrosidase for Gaucher disease.

Taliglucerase alfa is a hydrolytic lysosomal glucocerebrosidase-specific enzyme. Taliglucerase alpha catalyzes the hydrolysis of glucocerebroside to glucose and ceramide. Taliglucerase is thought to work by targeted delivery and uptake of tissue macrophages through the mannose lectin membrane system. Once inside the macrophage, taliglucerase degrades the accumulated glucocerebroside. Taliglucerase is not used to cure Gaucher disease, but to diminish the clinical manifestations of hepatosplenomegaly, and improve anemia and thrombocytopenia.

Elelyso (taliglucerase alfa) is indicated for long-term enzyme replacement therapy (ERT) for adults with a confirmed diagnosis of Type 1 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 endpoints were drug-related adverse events: Ab formation and hypersensitivity reactions. Primary efficacy endpoint was reduction in splenic volume measured by magnetic resonance imaging. Secondary endpoints were: changes in hemoglobin, hepatic volume, and platelet counts. 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 endpoints 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.

Anaphylaxis has been observed in some patients treated with Elelyso. If anaphylaxis occurs, immediately discontinue infusion and initiate appropriate treatment.

The most commonly observed symptoms of infusion reactions (including allergic reactions) were headache, chest pain or discomfort, asthenia, fatigue, urticarial, erythema, increased blood pressure, back pain, arthralgia, and flushing. If allergic
or infusion reactions occur, decreasing the infusion rate, temporarily stopping the infusion, or administering antihistamines and or antipyretics is recommended.

Taliglucerase alfa is available as Elelyso in 200 Unit single use vials for intravenous infusion. The recommended dose is 60 Units/kg of body weight administered every 2 weeks as a 60-120 minute intravenous infusion. Members currently being treated with imiglucerase for Type 1 Gaucher disease can be switched to Elelyso. Patients previously treated on a stable dose of imiglucerase are recommended to begin treatment with Elelyso at the same dose when they switch from imiglucerase to Elelyso.

Dose adjustments can be made based on achievement and maintenance of each member’s therapeutic goals. Clinical studies have evaluated dose ranges from 11 Units/kg to 73 Units/kg every other week.

Cerdelga (eliglustat) is an inhibitor of glucosylceramide synthase, where glucosylceramide is the primary substrate of β-glucosidase, the enzyme lacking in Gaucher disease. Historically, Gaucher cells are characterized by engorged macrophages, as glucosylceramide accumulates in these cells, causing cellular and organ dysfunction. Cerdelga (eliglustat) inhibits the formation of glucosylceramide, which helps to limit disease.

The U.S. Food and Drug Administration (FDA) approved eliglustat (Cerdelga) capsules for certain adult Gaucher disease type 1 patients (Genzyme, 2014) who are CYP2D6 poor metabolizers (PMs), intermediate metabolizers (IMs) or extensive metabolizers (EMs). Eliglustat 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 eliglustat: 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 eliglustat: spleen size, platelet levels, hemoglobin levels, and liver volume (Genzyme, 2014). Patients continue to receive eliglustat 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).

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.

Cerdelga (eliglustat) is available as 84 mg hard gelatin capsules. The recommended dose of Cerdelga (eliglustat) is 84 mg twice daily in CYP 2D6 IMs and EMs, with or without food. In PMs, the recommended dose is 84 mg once daily. Cerdelga (eliglustat) should not be used in CYP2D6 ultra-rapid metabolizers as they may not receive adequate serum concentrations of drug.

Cerdelga (eliglustat) therapy should be avoided in persons with the following concomitant conditions:

- Concurrent use of a strong or moderate CYP2D6 inhibitor (eg. paroxetine, terbinafine) with a strong or
moderate CYP3A inhibitor (eg. ketoconazole) in patients who are extensive metabolizers (Ems) or IMs (intermediate metabolizers)

- Concurrent use of a strong CYP3A inhibitor in patients who are intermediate metabolizers (IMs) or poor metabolizers (PMs) (eg. ketoconazole, fluconazole).

Mucopolysaccharidosis I (MPS I)

Aldurazyme (laronidase) is an enzyme replacement therapy for the treatment of mucopolysaccharidosis I (MPS I), a rare, autosomal recessive lysosomal storage disorder caused by a deficiency of the enzyme alpha-L-iduronidase. The lack of the enzyme causes glycosaminoglycans (GAG) to build up in cells. Manifestations of the disorder can include growth and developmental delay, enlargement of spleen and liver, skeletal deformity, cardiac and pulmonary impairment, vision or hearing loss and mental dysfunction.

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, hepatosplenicomegaly, 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.

Aldurazyme (laronidase) is indicated for enzyme replacement in patients with the Hurler and Hurler-Scheie forms of MPS I, and for Scheie patients with moderate to severe symptoms.

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.

Aldurazyme (laronidase) is available as 0.58 mg/mL solution for injection in a 5mL vial. Laronidase is administered intravenously once-weekly. The recommended dosage for laronidase is 0.58 mg/kg of body weight administered once weekly as an intravenous infusion. Pretreatment with antipyretics and/or antihistamines is recommended 60 minutes prior to the start of the infusion. 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.

Aldurazyme (laronidase) should be used with extreme caution and close monitoring, if at all, in any patient who has exhibited prior laronidase hypersensitivity.

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.

Fabrazyme (agalsidase beta) is a recombinant human α-galactosidase A enzyme indicated for the treatment of Fabry disease. 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 available as Fabrazyme (agalsidase beta) in 5mg and 35mg powder for injection. Agalsidase beta is administered by intravenous infusion every 2 weeks. The
The recommended dosage for agalsidase beta is 1.0 mg/kg IV every two weeks. 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**

Naglazyme (galsulfase) is a hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme indicated for patients with Mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy syndrome). MPS VI (Maroteaux-Lamy syndrome) is an autosomal recessive disorder that results from the deficiency of arylsulfatase B activity which is necessary for the breakdown of the glycosaminoglycans (GAGs). Cellular accumulation of GAG residues disrupt normal cell function, and result in progressive cellular, tissue, and organ dysfunction. Naglazyme (galsulfase) is indicated for the treatment of mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy syndrome).
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. While some patients have rapidly progressing disease, others do not present with signs and symptoms until adolescence. Yet, MPS VI-related multisystemic abnormalities and significant functional disability are life-altering. 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.

Naglazyme (galsulfase) is available in a 1mg/mL solution for injection in a 5mL vial. The recommended dose of Naglazyme (galsulfase) is 1 mg per kg of body weight administered once weekly as an intravenous infusion.

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.

Recombinant human alglucosidase alfa (rhGAA; Myozyme) provides exogenous human lysosomal acid alpha-glucosidase. Once available systemically, alglucosidase alfa mimics endogenous acid alpha-glucosidase. Alglucosidase alfa is indicated for use in members with Pompe disease (GAA deficiency).

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. Myozyme is indicated for the treatment of Pompe disease and has been shown to improve ventilator-free survival in members with infantile-onset
(initiated in children 1 month - 3.5 years) Pompe disease, use of Myozyme in members with other forms of Pompe disease has not been adequately studied to assure safety and efficacy.

Alglucosidase alpha (Myozyme) is available as a 50mg vial for reconstitution. Alglucosidase alfa (Genzyme Corp, Cambridge, MA) is administered by intravenous infusion every 2 weeks. The recommended dosage is 20 mg/kg body weight administered over approximately 4 hours as an intravenous infusion. The total volume of infusion is determined by the member's body weight.

Initiation of alglucosidase alfa therapy in the earliest stages of the disease process is associated with the most clinical benefit. Infusions should be administered in a stepwise manner using an infusion pump. The initial infusion rate should be no more than 1 mg/kg/hr. The infusion rate may be increased by 2 mg/kg/hr every 30 minutes, after member tolerance to the infusion rate is established, until a maximum rate of 7 mg/kg/hr is reached. Vital signs should be obtained at the end of each step.

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 aglucosidase 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. Strothotte 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.

Recombinant human alglucosidase alfa (rhGAA; Lumizyme) is a hydrolytic lysosomal glycogen-specific enzyme that provides exogenous human lysosomal acid alpha-glucosidase. Alglucosidase alfa is used primarily in members with Pompe
disease, which is an inherited disorder of glycogen metabolism caused by the relative or absolute absence of acid alpha-glucosidase. Once available systemically, alglucosidase alfa mimics endogenous acid alpha-glucosidase.

Alglucosidase alpha (Lumizyme) is available as a 50mg vial for reconstitution. The recommended dosage of alglucosidase alpha (Lumizyme) is 20 mg/kg body weight administered every 2 weeks as an intravenous infusion. The total volume of infusion is determined by the member’s body weight and should be administered over approximately 4 hours.

Initiation of alglucosidase alfa therapy in the earliest stages of the disease process is associated with the most clinical benefit. Infusions should be administered in a step-wise manner using an infusion pump. The initial infusion rate should be no more than 1mg/kg/hr. The infusion rate may be increased by 2 mg/kg/hr every 30 minutes, after member tolerance to the infusion rate is established, until a maximum rate of 7 mg/kg/hr is reached. Vital signs should be obtained at the end of each step. If the member is stable, Lumizyme may be administered at the maximum rate of 7 mg/kg/hr until the infusion is completed. The infusion rate may be slowed or temporarily stopped in the event of infusion reactions.

Hypersensitivity reactions have been observed in some patients during and after treatment with alglucosidase alfa. Ensure that appropriate medical support measures, including cardiopulmonary resuscitation equipment, are readily available. If anaphylaxis or severe hypersensitivity reactions occur, immediately discontinue infusion and initiate appropriate medical treatment.

Monitor patients for the development of systemic immune-mediated reactions involving skin and other organs.
Patients with compromised cardiac or respiratory function may be at risk of acute cardiorespiratory failure. Caution should be exercised when administering alglucosidase alfa to patients susceptible to fluid volume overload. Appropriate medical support and monitoring measures should be available during infusion.

There is a risk of cardiac arrhythmia and sudden cardiac death during general anesthesia for central venous catheter placement; caution should be used when administering general anesthesia for the placement of a central venous catheter intended for alglucosidase alfa infusion.

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.

Muenzer et al (2016) noted that approximately 2/3 of patients with the lysosomal storage disease MPS II have progressive cognitive impairment. Intravenous (i.v.) ERT does not affect cognitive impairment because recombinant iduronate-2-sulfatase (idursulfase) does not penetrate the BBB at therapeutic concentrations. In a phase I/II study, these researchers examined the safety of idursulfase formulated for intrathecal administration (idursulfase-IT) via intrathecal drug delivery device (IDDD). A secondary end-point was change in concentration of glycosaminoglycans in cerebro-spinal fluid (CSF). A total of 16 cognitively impaired males with mucopolysaccharidosis II who were previously treated with weekly i.v. idursulfase 0.5 mg/kg for greater than or equal to 6 months were enrolled. Patients were randomized to no treatment or 10-mg, 30-mg, or 1-mg idursulfase-IT monthly for 6 months (4 patients per group) while continuing i.v. idursulfase weekly. No serious adverse events related to idursulfase-IT were observed. Surgical revision/removal of the IDDD was required in 6 of 12 patients. Twelve total doses were administrated by lumbar puncture. Mean CSF glycosaminoglycan concentration was reduced by approximately 90% in the 10-mg and 30-mg groups and approximately 80% in the 1-mg group after 6 months. The authors concluded that these preliminary data supported further development of investigational idursulfase-IT in MPS II patients with the severe phenotype who have progressed only to a mild-to-moderate level of cognitive impairment.
Mu copolysaccharidosis IV (Morquio Syndrome)

Mu copolysaccharidosis IV (MPS IV A and B), also known as Morquio syndrome, is an autosomal recessive mucopolysaccharide storage disease. There are 2 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.

Vimizim (elosulfase alfa) is a hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme. The 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, aged 5 to 57 years. Patients were randomized to three treatment groups: elosulfase alfa 2 mg/kg once-weekly (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 6 minutes (6 minute walk test, 6-MWT) at Week 24. The other endpoints included changes from baseline in the rate of stair climbing in 3 minutes (3-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 to 40.9; p = 0.0174) in patients who received elosulfase 2 mg/kg once-weekly. There was no difference in the rate of stair climbing between patients who received elosulfase 2 mg/kg once-weekly 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; 173 of 176 patients enrolled in the extension trial in which patients received elosulfase 2 mg/kg once-weekly (n = 86) or elosulfase 2 mg/kg once every other week (n = 87). In patients who continued to receive elosulfase 2 mg/kg once-weekly 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. Anaphylaxis, presenting as cough, erythema, throat tightness, urticaria, flushing, cyanosis, hypotension, rash, dyspnea, chest discomfort, and gastrointestinal symptoms in conjunction with urticaria, have been reported to occur during infusions, regardless of duration of the course of treatment. Closely observe patients during and after Vimizim administration and be prepared to manage anaphylaxis. Inform patients of the signs and symptoms of anaphylaxis and have them seek immediate medical care should symptoms occur. Patients with acute respiratory illness may be at risk of serious acute exacerbation of their respiratory compromise due to hypersensitivity reactions, and require additional monitoring.

Elosulfase alfa is available as Vimizim in 5 mg/5 mL single-use vials for intravenous infusion. The recommended dose of elosulfase alfa is 2 mg/kg given intravenously over a minimum range of 3.5 to 4.5 hours, based on infusion volume, once every week.

Lysosomal Acid Lipase Deficiency

Kanuma (sebelipase alfa) is a recombinant human lysosomal acid lipase (rhLAL). It is produced by recombinant DNA technology in the egg white of eggs laid by genetically engineered chickens. The FDA approved sebelipase alfa (Kanuma) for the treatment of patients with a diagnosis of lysosomal acid lipase deficiency (LAL-D).
LAL-D is a genetic, chronic, and progressive metabolic disease that may be associated with significant morbidity and premature mortality. It is an ultra-rare disease, which is defined as a disease that affects fewer than 20 patients/1,000,000 of the general population.

LAL-D is caused by genetic mutations that result in a marked decrease or loss in LAL enzyme activity in the lysosomes across multiple body tissues, leading to the chronic build-up of cholesteryl esters and triglycerides in the liver, blood vessel walls, and other organs. Without treatment, the youngest patients with LAL-D face rapid disease progression that is typically fatal within a matter of months. Infants experience profound growth failure, liver fibrosis, and cirrhosis, with a median age of death at 3.7 months. In an observational study, approximately 50% of children and adults with LAL-D progressed to fibrosis, cirrhosis, or liver transplant in 3 years. The median age of onset of LAL-D is 5.8 years. Many older patients may be asymptomatic with increased risk of development of fibrosis, cirrhosis, liver failure, accelerated atherosclerosis, and cardiovascular disease.

There were no approved therapies available to treatment patients with LAL deficiency. The standard of care prior to approval of sebelipase alfa was supportive care, including lipid lowering therapies, vitamine E, hematopoietic stem cell (HSCT), and liver transplantation.

Measurement of LAL activity can be performed with a Dried Blood Spot (DBS) test using the fluorimetric substrate 4-methylumbelliferyl palmitate. Dried blood spot LAL enzyme testing was the primary methodology used in the clinical development program (including the pivotal trials).

Sebelipase alfa is an enzyme replacement therapy that addresses the underlying cause of lysosomal acid lipase deficiency (LAL-D) by reducing substrate accumulation in the lysosomes of cells throughout the body. Sebelipase alfa binds
to cell surface receptors via glycans expressed on the protein and is subsequently internalized into lysosomes. Sebelipase alfa catalyzes the lysosomal hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol and free fatty acids, enzyme. In clinical studies, treatment with Kanuma improved survival in infants with LAL-D and led to significant reductions in ALT and liver fat content, as well as significant improvements in lipid parameters, in children and adults with LAL-D.

The FDA approval of sebelipase alfa was based on data from two clinical studies and a supporting open-label extension study comprising infant, pediatric, and adult patients with LAL-D. Study results showed significant benefit in terms of survival (67%, or 6 out of 9) in patients with the infant form of LAL-D beyond 12 months, compared with 0 out of 21 patients in an untreated historical cohort. In pediatric and adult patients with LAL-D (aged 4 to 58 years), treatment with sebelipase alfa resulted in larger reductions from baseline in ALT values and liver fat content, as measured by MRI, compared to treatment with placebo. In addition, treated patients had significant improvements in lipid parameters, including LDL-C, HDL-C, non-HDL-C, and triglycerides, compared to placebo. The significance of these findings as they relate to cardiovascular morbidity and mortality or progression of liver disease in LAL deficiency has not been established.

The most commonly reported adverse events observed in clinical trials in infants were diarrhea, vomiting, fever, rhinitis, anemia, cough, nasopharyngitis, and urticaria. The most commonly reported adverse events observed in clinical trials in pediatric and adult patients were headache, fever, oropharyngeal pain, nasopharyngitis, asthenia, constipation, and nausea.
Hypersensitivity reactions, including anaphylaxis, have been reported in patients treated with sebelipase alfa. In clinical trials, 3 of 106 (3%) patients treated with sebelipase alfa experienced signs and symptoms consistent with anaphylaxis. These patients experienced reactions during infusion with signs and symptoms including chest discomfort, conjunctival injection, dyspnea, generalized and itchy rash, hyperemia, swelling of eyelids, rhinorrhea, severe respiratory distress, tachycardia, tachypnea, and urticaria. Anaphylaxis has occurred as early as the sixth infusion and as late as 1 year after treatment initiation.

In clinical trials, 21 of 106 (20%) sebelipase-treated patients, including 9 of 14 (64%) infants and 12 of 92 (13%) pediatric patients, 4 years and older, and adults experienced signs and symptoms either consistent with or that may be related to a hypersensitivity reaction. Signs and symptoms of hypersensitivity reactions, occurring in 2 or more patients, included abdominal pain, agitation, fever, chills, diarrhea, eczema, edema, hypertension, irritability, laryngeal edema, nausea, pallor, pruritus, rash, and vomiting. The majority of reactions occurred during or within 4 hours of the completion of the infusion. Patients were not routinely pre-medicated prior to infusion of sebelipase in these clinical trials.

Due to the potential for anaphylaxis, the labeling states that appropriate medical support should be readily available when sebelipase alfa is administered.

The labeling states that the risks and benefits of treatment of sebelipase alfa in patients with known systemic hypersensitivity reactions to eggs or egg products.

The most common adverse reactions are: In patients with rapidly progressive disease presenting within the first 6 months of life (greater than or equal to 30%): diarrhea, vomiting, fever, rhinitis, anemia, cough, nasopharyngitis, and
urticaria. In pediatric and adult patients (greater than or equal to 8%): headache, fever, oropharyngeal pain, nasopharyngitis, asthenia, constipation, and nausea.

Sebelipase alfa is available as Kanuma 20 mg/10 mL solution in single-use vials for intravenous infusion. For patients with rapidly progressive LAL deficiency presenting within the first 6 months of life, the recommended starting dosage is 1 mg/kg as an intravenous infusion once weekly. For patients who do not achieve an optimal clinical response, increase to 3 mg/kg once-weekly.

For pediatric and adult patients with LAL deficiency, the recommended dosage is 1 mg/kg as an intravenous infusion once every other week.

Miscellaneous Treatments of Mucopolysaccharidoses

Ishii et al (2012) stated that Fabry disease is an inherited lysosomal storage disorder caused by deficient α-galactosidase A activity. Many missense mutations in Fabry disease often cause misfolded gene products, which leads to their retention in the endoplasmic reticulum by the quality control system; they are then removed by endoplasmic reticulum-associated degradation. These researchers discovered that a potent α-galactosidase A inhibitor, 1-deoxygalactonojirimycin, acts as a pharmacological chaperone to facilitate the proper folding of the mutant enzyme by binding to its active site, thereby improving its stability and trafficking to the lysosomes in mammalian cells. The oral administration of 1-deoxygalactonojirimycin to transgenic mice expressing human mutant α-galactosidase A resulted in significant increases in α-galactosidase A activity in various organs, with concomitant reductions in globotriaosylceramide, which contributes to the pathology of Fabry disease. A total of 78 missense mutations were found to be responsive to
1-deoxygalactonojirimycin. The authors concluded that these data indicated that many patients with Fabry disease could potentially benefit from pharmacological chaperone therapy.

Noh and Lee (2014) noted that MPSs are a group of rare inherited metabolic diseases caused by genetic defects in the production of lysosomal enzymes. Mucopolysaccharidoses are clinically heterogeneous and are characterized by progressive deterioration in visceral, skeletal and neurological functions. These investigators reviewed the classification and pathophysiology of MPSs and discussed current therapies and new targeted agents under development. They performed a Medline search through PubMed for relevant articles and treatment guidelines on MPSs published in English for years 1970 to September of 2013 inclusive. The references listed in the identified articles, prescribing information of the drugs approved for the treatment of MPSs, as well as recent clinical trial information posted on Clinicaltrials.gov website, were reviewed. Until recently, supportive care was the only option available for the management of MPSs. In the early 2000s, ERT was approved by the FDA for the treatment of MPS I, II and VI. Clinical trials of ERT showed substantial improvements in patients' somatic symptoms; however, no benefit was found in the neurological symptoms because the enzymes do not readily cross the blood-brain barrier (BBB). Hematopoietic stem cell transplantation (HSCT), another potentially curative treatment, is not routinely advocated in clinical practice due to its high risk profile and lack of evidence for efficacy, except in preserving cognition and prolonging survival in young patients with severe MPS I. In recent years, substrate reduction therapy (SRT) and gene therapy have been rapidly gaining greater recognition as potential therapeutic avenues. Substrate reduction therapy uses an orally available, small molecule drug (e.g., miglustat or eliglustat) that inhibits the first committed step in glycosphingolipid biosynthesis. The objective is to reduce the rate of biosynthesis of glycosphingolipids to offset the catabolic defect, restoring the balance between the rate of
biosynthesis and the rate of catabolism. The authors concluded that ERT is effective for the treatment of many somatic symptoms, particularly walking ability and respiratory function, and remains the mainstay of MPS treatment. They stated that the usefulness of HSCT has not been established adequately for most MPSs. Although still under investigation, SRT and gene therapy are promising MPS treatments that may prevent the neurodegeneration not affected by ERT.

Parenti et al (2014) stated that pharmacological chaperone therapy is an emerging approach to treat lysosomal storage diseases. Small-molecule chaperones interact with mutant enzymes, favor their correct conformation and enhance their stability. This approach showed significant advantages when compared with existing therapies, particularly in terms of the bioavailability of drugs, oral administration and positive impact on the quality of patients' lives. On the other hand, future research in this field must confront important challenges. The identification of novel chaperones is indispensable to expanding the number of patients amenable to this treatment and to optimize therapeutic efficacy. It is important to develop new allosteric drugs, to address the risk of inhibiting target enzymes. The authors concluded that future research must also be directed towards the exploitation of synergies between chaperone treatment and other therapeutic approaches.

Parenti et al (2015) stated that lysosomal storage diseases are a group of rare, inborn, metabolic errors characterized by deficiencies in normal lysosomal function and by intra-lysosomal accumulation of un-degraded substrates. The past 25 years have been characterized by remarkable progress in the treatment of these diseases and by the development of multiple therapeutic approaches. These approaches include strategies aimed at increasing the residual activity of a missing enzyme (ERT, HSCT, pharmacological chaperone therapy and gene therapy) and approaches based on reducing the flux of substrates to lysosomes.
An UpToDate review on “Gaucher disease: Treatment” (Hughes, 2015) states that “Enzyme-enhancement therapy (EET), which attempts to increase the residual function of mutant enzymes, is another potential future therapy for GD. In EET, pharmacologic or chemical chaperones are used to stabilize folding of mutant glucocerebrosidase or decrease its degradation. Chemical chaperones for the treatment of GD have been evaluated in clinical trials, but the development program of the lead compound GD (afegostat tartrate) was suspended as a result of lack of efficacy.”

Giugliani et al (2016) stated that mucopolysaccharidoses MPSs are progressive, usually severe, and, in a significant number of cases, involve cognitive impairment. These investigators noted that this review would not cover established treatments (e.g., bone marrow/hematopoietic stem cell transplantation and classic intravenous ERT), whose long-term outcomes have already been published (MPS I, MPS II, and MPS VI), instead, it focused on emerging therapies for MPSs, which includes intravenous ERT for MPS IVA and VII, intrathecal ERT, ERT with fusion proteins, substrate reduction therapy, gene therapy, and other novel approaches.

Gaucher Disease:

Pastores and colleagues (2016) noted that anti-drug antibodies (ADA) may develop with biological therapies, possibly leading to a reduction of treatment efficacy and to allergic and other adverse reactions. Patients with Gaucher disease were tested for ADA every 6 or 12 weeks in clinical studies of velaglucerase alfa ERT, as part of a range of safety endpoints. In 10 studies between April 2004 and March 2015, a total of 289 patients aged 2 to 84 years (median of 43) were assessed for the development of anti-velaglucerase alfa antibodies; 64 patients were treatment-naïve at baseline and 225 patients were switched to velaglucerase alfa from imiglucerase treatment. They received velaglucerase alfa treatment for a median of 36.4 weeks (interquartile range [IQR]
26.4 to 155.4 weeks); 4 patients (1.4%) became positive for anti-velaglucerase alfa IgG antibodies, 2 of whom had antibodies that were neutralizing in-vitro, but there were no apparent changes in patients' platelet counts, hemoglobin levels or levels of CCL18 and chitotriosidase, suggestive of clinical deterioration after anti-velaglucerase alfa antibodies were detected, and no infusion-related adverse events (AEs) were reported. The authors concluded that less than 2% of patients exposed to velaglucerase alfa tested positive for antibodies and there was no apparent correlation between anti-velaglucerase alfa antibodies and AEs or pharmacodynamics or clinical responses.

*Mucopolysaccharidosis I (MPS I):*

Xue and colleagues (2016) stated that ERT with laronidase has an important role in the treatment of patients with MPS I. Laronidase is safe and has demonstrated effectiveness in terms of stabilizing or improving conventional clinical and laboratory markers of the disease. However, like most ERTs, laronidase produces an anti-drug IgG antibody response in more than 90% of patients during the first few months of treatment. Pre-clinical data from the MPS I canine model suggested that ADA impair enzyme uptake in target tissues. In patients, the effects on tissue glycosaminoglycan (GAG) clearance are difficult to evaluate directly; but data from clinical studies have suggested an association between ADA and both a reduced pharmacodynamics response and hypersensitivity reactions. The authors carried out a comprehensive meta-analysis of pooled data from patients in 3 clinical studies of laronidase (including 1 study with an extension) to provide a more robust assessment of the relationship between the ADA response to laronidase, clinical and laboratory markers of MPS I, and hypersensitivity reactions. The meta-analysis demonstrated an inverse relationship between the ADA response and the percent reduction in urinary GAG (uGAG) levels. However, no relationships between the ADA response and changes in percent predicted forced vital capacity and...
6-minute walk test were seen. The study also re-assayed stored serum samples from the original trials with a novel method to determine the inhibitory effect of ADA. Patients with higher ADA exposure over time were found to have higher inhibition of enzyme uptake into cells. The authors concluded that high ADA exposure could result in a commensurate level of enzyme uptake inhibition that decreases the pharmacodynamics effect of the exogenously administered therapeutic enzyme, but with no clear effect on clinical efficacy.

*Fabry Disease:*

Pisani and co-workers (2017) noted that in 2009, the agalsidase beta shortage resulted in switching to agalsidase alfa treatment for many Fabry disease patients, offering the unique opportunity to compare the effects of the 2 drugs. Because single studies describing effects of switching on the disease course were limited and inconclusive, these researchers performed a systematic review and meta-analysis of existing data. Relevant studies were identified in the PubMed, Cochrane, ISI Web, and SCOPUS databases from July 2009 to September 2015. The following parameters were analyzed: clinical events, changes in organ function or structure, disease-related symptoms, lyso-Gb3 plasma levels, and AEs. The 9 studies (217 patients) included in this systematic review showed only marginal differences in most of the evaluated parameters; 7 of these studies were included in the meta-analysis (176 patients). The pooled incidence rate of major AEs was reported for 5 studies (150 patients) and was equal to 0.04 events per person-year. No significant change was observed after the shift in glomerular filtration rate, whereas left ventricular mass index, left ventricular posterior wall dimension, and ejection fraction were significantly reduced over time. The authors concluded that these findings showed that the switch to agalsidase alfa was well-tolerated and associated with stable clinical conditions.
Hunter Syndrome:

In a 109-week, non-randomized, observational study of MPS II patients already enrolled in the Hunter Outcome Survey (HOS), Giugliani and associates (2017) evaluated the long-term immunogenicity of idursulfase, and examined the effect of idursulfase-specific antibody generation on treatment safety (via infusion-related adverse events [IRAEs]) and pharmacodynamics (via urinary glycosaminoglycans [uGAGs]). Male patients greater than or equal to 5 years, enrolled in HOS regardless of idursulfase treatment status were eligible. Blood/urine samples for anti-idursulfase antibody testing and uGAG measurement were collected every 12 weeks. Due to difficulties in enrolling treatment-naïve patients, data collection was limited to 26 enrolled patients of 100 planned patients (aged 5.1 to 35.5 years) all of whom were non-naïve to treatment; 15 (58%) patients completed the study. There were 11/26 (42%) sero-positive patients at baseline (Ab +), and 2/26 (8%) others developed intermittent sero-positivity by week 13. A total of 9/26 patients (35%) had greater than or equal to 1 sample positive for neutralizing antibodies. Baseline uGAG levels were low due to prior idursulfase treatment and did not change appreciably thereafter. Ab + patients had persistently higher uGAG levels at entry and throughout the study than Ab – patients; 9 of 26 (34%) patients reported IRAEs. Ab + patients appeared to have a higher risk of developing IRAEs than Ab - patients. However, the relative risk (RR) was not statistically significant and decreased after adjustment for age. The authors concluded that 50% of study patients developed idursulfase antibodies; notably Ab + patients had persistently higher average uGAG levels; however, a clear association between IRAEs and antibodies was not established.

Mucopolysaccharidosis IV (Morquio Syndrome):
Melton and colleagues (2017) stated that many ERTs for lysosomal storage disorders use the cell-surface cation-independent mannose-6 phosphate receptor (CI-M6PR) to deliver ERTs to the lysosome. However, neutralizing antibodies (NAb) may interfere with this process. These researchers previously reported that most individuals with Morquio A who received elosulfase alfa in the phase III MOR-004 trial tested positive for NAbS capable of interfering with binding to CI-M6PR ectodomain in an ELISA-based assay. However, no correlation was detected between NAb occurrence and clinical efficacy or pharmacodynamics. To quantify and better characterize the impact of NAbS, these investigators developed a functional cell-based flow cytometry assay with a titer step that detects antibodies capable of interfering with elosulfase alfa uptake. Serum samples collected during the MOR-004 trial were tested and titers were determined. Consistent with earlier findings on NAb positivity, no correlations were observed between NAb titers and the clinical outcomes of elosulfase alfa-treated individuals with Morquio A.

Late Infantile Neuronal Ceroid Lipofuscinosis type 2 (CLN2)

The U.S. Food and Drug Administration (FDA) approved cerliponase alfa (Brineura) to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency, a form of Batten disease.

CLN2 disease is an rare, rapidly progressive fatal brain condition, which affects less than one in one million U.S. residents. Every year approximately 20 children are born in the U.S. with CLN2 disease. These affected children completely lose the ability to walk and talk around 6 years of
age. During the later stages of the disease, feeding and tending to everyday needs become very difficult with death often occurring between 8 and 12 years of age.

Children with CLN2 disease typically begin experiencing seizures between the ages of 2 and 4 years old, preceded in the majority of cases by language development delay. The disease progresses rapidly with most affected children losing the ability to walk and talk by approximately 6 years of age. Initial symptoms are followed by movement disorders, motor deterioration, dementia, blindness, and death usually occurring between the ages of 8 and 12 years of age. During the later stages of the disease, feeding and tending to everyday needs become very difficult.

The neuronal ceroid lipofuscinoses (NCLs) are a heterogeneous group of lysosomal storage disorders that includes the autosomal recessive neurodegenerative disorder CLN2 disease. CLN2 disease is caused by mutations in the TPP1 gene resulting in deficient activity of the enzyme tripeptidyl peptidase 1 (TPP1). In the absence of TPP1, lysosomal storage materials normally metabolized by this enzyme accumulate in many organs, particularly in the brain and retina. Buildup of these storage materials in the cells of the nervous system contribute to the progressive and relentless neurodegeneration which manifests as loss of cognitive, motor, and visual functions.

Cerliponase alfa is a recombinant form of human tripeptidyl peptidase 1 (TPP1), the enzyme deficient in patients with CLN2 disease. It is an enzyme replacement therapy designed to restore TPP1 enzyme activity and break down the storage materials that cause CLN2 disease. In order to reach the cells of the brain and central nervous system, the treatment is delivered directly into the fluid surrounding the brain (cerebrospinal fluid) using BioMarin’s patented technology.
Cerliponase alfa is a prescription medication used to slow loss of ability to walk or crawl (ambulation) in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency.

In clinical trials, cerliponase alfa, an enzyme replacement therapy, was shown to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with CLN2 disease. It is the first enzyme replacement therapy to be directly administered to the brain, treating the underlying cause of the condition by replacing the deficient TPP1 enzyme. Using an established technique most often used in oncology—intraventricular administration—the therapy is delivered directly into fluid surrounding the brain, known as the cerebrospinal fluid.

The approval was supported by safety and efficacy data assessed over 96 weeks in a non-randomized, single-arm dose escalation clinical study of patients with CLN2 disease. Cerliponase alfa treated patients were compared to untreated patients from a natural history cohort.

Patients were assessed for decline in the motor domain of the CLN2 Clinical Rating Scale. The scale measures performance of mobility with normal function being a score of 3 and no function being a score of 0. Decline was defined as having a sustained 2-point decline or an unreversed score of 0 in the motor domain of the CLN2 Clinical Rating Scale.

Twenty-four patients aged 3-8 years were enrolled in the clinical study. One patient withdrew after week 1 due to inability to continue with study procedures; 23 patients were treated with cerliponase alfa every other week for 48 weeks and continued treatment during the extension.
Results from the 96-week analysis demonstrated the odds of cerliponase alfa-treated patients not having a decline were 13 times the odds of natural history cohort patients not having a decline (Odds Ratio (95% Confidence Interval): 13.1 (1.2, 146.9)).

Of the 22 patients treated with cerliponase alfa and evaluated for efficacy at week 96, 21 (95%) did not decline, and only the patient who terminated early was deemed to have a decline in the motor domain of the CLN2 Clinical Rating Scale. In comparison, 50% of patients in an independent natural history cohort demonstrated progressive decline in motor function. Two cerliponase alfa treated patients with a maximum score were excluded from the analyses; they maintained that score throughout the study period.

In the clinical study, intraventricular access device-related infections were observed in two patients. In each case, antibiotics were administered, the intraventricular access device was replaced and the patient continued on cerliponase alfa treatment. Hypotension was reported in 2 (8%) patients, which occurred during or up to 8 hours after cerliponase alfa infusion. Patients did not require alteration in treatment and reactions resolved spontaneously or after IV fluid administration.

Hypersensitivity reactions have been reported in 11 (46%) cerliponase alfa treated patients during the clinical studies. The most common adverse reactions (≥8%) are pyrexia, ECG abnormalities, decreased cerebrospinal fluid (CSF) protein, vomiting, seizures, hypersensitivity, increased CSF protein, hematoma, headache, irritability, pleocytosis, device-related infection, bradycardia, feeling jittery, and hypotension.

Cerliponase alfa is a prescription medicine. Before treatment with cerliponase alfa, it is important to discuss your child's medical history with their doctor. Tell the doctor if they are sick or taking any medication and if they are allergic to any
medicines. Your child's doctor will decide if cerliponase alfa is right for them. If you have questions or would like more information about cerliponase alfa, contact your child's doctor.

Cerliponase alfa is only given by infusion into the fluid of the brain (known as an intraventricular injection) and using sterile technique to reduce the risk of infection. An intraventricular access device or port must be in place at least 5 to 7 days prior to the first infusion. Intraventricular access device-related infections were observed with cerliponase alfa treatment. If any signs of infection occur, contact your child's doctor immediately. Your child's intraventricular access device may need to be replaced over time.

Cerliponase alfa should not be used in patients with active intraventricular access device-related complications (e.g., leakage, device failure, or device-related infection) and with shunts used to drain extra fluid around the brain.

Low blood pressure and/or slow heart rate may occur during and following the cerliponase alfa infusion. Contact your child's doctor immediately if these reactions occur.

Undesirable or hypersensitivity reactions related to cerliponase alfa treatment, including fever, vomiting, and irritability, may occur during treatment and as late as 24 hours after infusion. Your child may receive medication such as antihistamines before cerliponase alfa infusions to reduce the risk of reactions. Serious and severe allergic reactions (anaphylaxis) may occur. If a reaction occurs, the infusion will be stopped and your child may be given additional medication. If a severe reaction occurs, the infusion will be stopped and your child will receive appropriate medical treatment. If any signs of anaphylaxis occur, immediately seek medical care.

Safety and effectiveness in pediatric patients below 3 years of age have not been established.
The most common side effects reported during cerliponase alfa infusions included fever, problems with the electrical activity of the heart, decreased or increased protein in the fluid of the brain, vomiting, seizures, hypersensitivity, collection of blood outside of blood vessels (hematoma), headache, irritability, and increased white blood cell count in the fluid of the brain, device-related infection, slow heart rate, feeling jittery, and low blood pressure. Intraventricular device-related side effects included infection, delivery system-related complications, and increased white blood cell count in fluid of the brain.

The recommended dosage is 300 mg administered once every other week as an intraventricular infusion followed by infusion of Intraventricular Electrolytes over approximately 4.5 hours.

Mucopolysaccharidoses type VII (MPS 7) (Sly Syndrome)

MPS VII is an autosomal recessive lysosomal storage disorder caused by deficiency of beta-glucuronidase (NORD, 2017). The deficiency in beta-glucuronidase leads to the accumulation of mucopolysaccharides in many tissues and organs of the body. MPS VII affects less than 150 patients worldwide (FDA, 2017). The features of MPS VII vary, but most affected individuals have skeletal abnormalities that become more pronounced with age, including short stature and changes in bones visible on X-rays (dysostosis multiplex). Patients can also develop aortic regurgitation, hepatomegaly, splenomegaly, and narrowed airways which can lead to pulmonary infections and trouble breathing. The life expectancy of individuals with MPS VII depends on the severity of symptoms. Some affected individuals do not survive infancy, while others may live into adolescence or adulthood. Heart disease and airway obstruction are major causes of death in people with MPS VII. Affected individuals may have developmental delay and progressive intellectual disability.

Urinary levels of the mucopolysaccharides (dermatan sulfate,
heparan sulfate, and chondroitin sulfate) are increased in affected individuals (NORD, 2017). The diagnosis of MPS VII may be confirmed by specialized tests that measure the level of beta-glucuronidase activity in blood or skin cells. Molecular genetic testing for mutations in the GUSB gene is available to confirm the diagnosis.

The U.S. Food and Drug Administration (FDA) approved vestronidase alfa-vjbk (Mepsevii) to treat pediatric and adult patients with an MPS VII (FDA, 2017). The safety and efficacy of vestronidase alfa-vjbk were established in clinical trial and expanded access protocols enrolling a total of 23 patients ranging from 5 months to 25 years of age. Patients received treatment with vestronidase alfa-vjbk at doses up to 4 mg/kg once every two weeks for up to 164 weeks. Efficacy was primarily assessed via the six-minute walk test in ten patients who could perform the test. After 24 weeks of treatment, the mean difference in distance walked relative to placebo was 18 meters. Additional follow-up for up to 120 weeks suggested continued improvement in three patients and stabilization in the others. Two patients in the vestronidase alfa-vjbk development program experienced marked improvement in pulmonary function. The product labeling for Mepsevii states that the effect of vestronidase alfa-vjbk on the central nervous system manifestations of MPS VII has not been determined.

The FDA is requiring the manufacturer to conduct a post-marketing study to evaluate the long-term safety of the product (FDA, 2017).

The most common side effects after treatment with vestronidase alfa-vjbk include infusion site reactions, diarrhea, rash and anaphylaxis (FDA, 2017).

The labeling includes a black box warning about anaphylaxis with Mepsevii administration (Ultragenyx, 2017).
Mepsevii is available as 10 mg/5 mL (2 mg/mL) in a single-dose vial (Ultragenyx, 2017). The recommended dosage is 4 mg/kg administered every two weeks as an intravenous infusion.

Anderson-Fabry Disease

El Dib and colleagues (2017) stated that Anderson-Fabry disease (AFD) is an X-linked recessive inborn error of glycosphingolipid metabolism caused by a deficiency of alpha-galactosidase A. Renal failure, heart and cerebrovascular involvement reduce survival. A Cochrane review provided little evidence on the use of ERT. These investigators complemented this review through a linear regression and a pooled analysis of proportions from cohort studies. They evaluated the safety and efficacy of ERT for AFD. For the systematic review, a literature search was performed, from inception to March 2016, using Medline, Embase and LILACS. Inclusion criteria were cohort studies, patients with AFD on ERT or natural history, and at least 1 patient-important outcome (all-cause mortality, renal, cardiovascular or cerebrovascular events, and AEs) reported. The pooled proportion and the CI were shown for each outcome. Simple linear regressions for composite endpoints were performed. A total of 77 cohort studies involving 15,305 participants proved eligible. The pooled proportions were as follows: For renal complications, agalsidase alfa 15.3 % [95 % CI: 0.048 to 0.303; I² = 77.2 %, p = 0.0005]; agalsidase beta 6 % [95 % CI: 0.04 to 0.07; I² = not applicable]; and untreated patients 21.4 % [95 % CI: 0.1522 to 0.2835; I² = 89.6 %, p < 0.0001]. Effect differences favored agalsidase beta compared to untreated patients; for cardiovascular complications, agalsidase alfa 28 % [95 % CI: 0.07 to 0.55; I² = 96.7 %, p < 0.0001]; agalsidase beta 7 % [95 % CI: 0.05 to 0.08; I² = not applicable]; and untreated patients 26.2 % [95 % CI: 0.149 to 0.394; I² = 98.8 %, p < 0.0001]. Effect differences favored agalsidase beta compared to untreated patients; and for cerebrovascular complications, agalsidase alfa 11.1 % [95 % CI: 0.058 to
0.179; I² = 70.5 %, p = 0.0024]; agalsidase beta 3.5 % [95 % CI: 0.024 to 0.046; I² = 0 %, p = 0.4209]; and untreated patients 18.3 % [95 % CI: 0.129 to 0.245; I² = 95 % p < 0.0001]. Effect differences favored agalsidase beta over agalsidase alfa or untreated patients. A linear regression showed that Fabry patients receiving agalsidase alfa were more likely to have higher rates of composite end-points compared to those receiving agalsidase beta. The authors concluded that agalsidase beta was associated with a significantly lower incidence of renal, cardiovascular and cerebrovascular events than no ERT, and to a significantly lower incidence of cerebrovascular events than agalsidase alfa. They stated that in view of these results, the use of agalsidase beta for preventing major organ complications related to AFD can be recommended.

Hematopoietic Stem Cell Therapy

Biffi (2017) stated that lysosomal storage disorders (LSDs) are a broad class of monogenic diseases with an overall incidence of 1:7,000 newborns, due to the defective activity of one or more lysosomal hydrolases or related proteins resulting in storage of un-degraded substrates in the lysosomes. The over 40 different known LSDs share a life-threatening nature, but they are present with extremely variable clinical manifestations, determined by the characteristics and tissue distribution of the material accumulating due to the lysosomal dysfunction. The majority of LSDs lack a curative treatment. This is particularly true for LSDs severely affecting the central nervous system (CNS). Based on current pre-clinical and clinical evidences, among other treatment modalities, hematopoietic stem cell therapy (HSCT) could potentially result in robust therapeutic benefit for LSD patients, with particular indication for those characterized by severe brain damage. The authors concluded that optimization of current approaches and technology, as well as implementation of
clinical trials for novel indications, and prolonged and more extensive follow-up of the already treated patients will allow translating this promise into new medicinal products.

Azario and associates (2017) noted that umbilical cord blood (UCB) is a promising source of stem cells to use in early HSCT approaches for several genetic diseases that can be diagnosed at birth. Mucopolysaccharidosis type I (MPS-I) is a progressive multi-system disorder caused by deficiency of lysosomal enzyme α-L-iduronidase, and patients treated with allogeneic HSCT at the onset have improved outcome, suggesting to administer such therapy as early as possible. Given that the best characterized MPS-I murine model is an immunocompetent mouse, these researchers developed a transplantation system based on murine UCB. With the final aim of testing the therapeutic efficacy of UCB in MPS-I mice transplanted at birth, these investigators first defined the features of murine UCB cells and demonstrated that they were capable of multi-lineage hematopoietic re-population of myelo-ablated adult mice similarly to bone marrow cells. They then assessed the effectiveness of murine UCB cells transplantation in busulfan-conditioned newborn MPS-I mice; 20 weeks after treatment, iduronidase activity was increased in visceral organs of MPS-I animals, glycosaminoglycans storage was reduced, and skeletal phenotype was ameliorated. The authors concluded that this study explored a potential therapy for MPS-I at a very early stage in life and represents a novel model to test UCB-based transplantation approaches for various diseases.

Somaraju and Tadepalli (2017) stated that Gaucher disease is the most common LSD caused by a deficiency of the enzyme glucocerebrosidase. Current treatment of the disease involves a choice from ERT, substrate reduction therapy and HSCT. Hematopoietic stem cell therapy is a high risk procedure with possible long-term benefits in the regression of skeletal and neurological changes in people with Gaucher disease. This is an update of a previously published Cochrane Review. These
investigators determined the role of HSCT in people with Gaucher disease in relation to: mortality risk associated with the procedure; efficacy in modifying the course of the disease; and arrest or regression of neurological manifestations in neuronopathic forms (types 2 and 3). They searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Inborn Errors of Metabolism Trials Register which comprises of references identified from comprehensive electronic database searches and hand-searches of relevant journals and abstract books of conference proceedings. Date of the most recent search of the Group's Hemoglobinopathies Trials Register: January 19, 2017. These investigators also searched the websites: www.clinicaltrials.gov; WHO International Clinical Trials Registry Platform portal and www.genzymeclinicalresearch.com. Date of most recent search of these sites: 02 March 2017. All randomized, quasi-randomized and controlled clinical trials comparing SCT with ERT, substrate reduction therapy, symptomatic treatment or no treatment in people with Gaucher disease of all ages were selected for analysis. The authors independently assessed trials for inclusion, however, no relevant trials were identified. A total of 32 trials were identified by the searches; however, these were not suitable for inclusion in the review. The authors concluded that HSCT is a form of treatment that offers the potential of permanent cure. However, there were no clinical trials that have assessed the safety and efficacy of this treatment in comparison to other conservative measures (ERT, substrate reduction therapy) now in use. There were no trials included in the review and these researchers had not identified any relevant trials up to March 2017.

Wright and colleagues (2017) described long-term outcomes of children with early-infantile Krabbe disease who underwent HSCT in the first 7 weeks of life. In this prospective longitudinal study, evaluations were performed at baseline and follow-up included brain imaging, neuro-diagnostic tests, and neuro-behavioral evaluations. Of the 18 patients in this study (11 girls, 7 boys; mean follow-up of 9.5 years, range of 4 to
15), 5 died (3 of peri-transplant complications, 1 of a surgical complication unrelated to Krabbe disease, 1 of disease progression); 1 of the surviving patients had normal cognitive function and 10 continue to develop cognitive skills at a slightly slower rate than normal. All surviving patients continue to gain receptive language skills, with 7 falling within the normal range; 10 patients received speech therapy, and 2 of these patients required augmentative communication devices. Gross motor development varies widely, but 3 patients could walk independently, and 7 walked with assistive devices. Spasticity ranged from mild to severe, and 12 patients wore orthotics. Fine motor skills were generally preserved. Brain myelination and atrophy stabilized in 8 patients, improved in 4 patients, and worsened in 1 patient. Nerve conduction velocities initially improved but continued to be abnormal in most patients. The authors concluded that surviving patients functioned at a much higher level than untreated children or symptomatic children who underwent HSCT. They stated that these results showed that early HSCT changed the natural history of this disease by improving both lifespan and functional abilities. Moreover, the authors stated that continued follow-up studies are needed to monitor the long-term outcomes of treated patients as they age into adolescence and young adulthood. It will also be critical to identify a pre-symptomatic diagnostic biomarker that will enable clinicians to confidently follow babies at moderate and high risk for Krabbe disease identified through newborn screening programs and those treated with HSCT or any other future therapies. This study provided Class IV evidence that for children with early-infantile Krabbe disease, early HSCT improved lifespan and functional abilities.

Metallothioneins

Cavalca and colleagues (2018) noted that LSDs are a broad class of inherited metabolic diseases caused by the defective activity of lysosomal enzymes; CNS manifestations are present in roughly 50% of LSD patients and represent an
unmet medical need for them. These researchers examined the therapeutic potential of metallothioneins (MTs), a newly identified family of proteins with reported neuroprotective roles, in the murine models of 2 LSDs with CNS involvement. MT-1 over-expressing transgenic mice (MTtg) were crossed with the murine models of Batten and Krabbe diseases. Changes in the survival and manifestations of the disease in the MTtg setting were assessed. In addition, these researchers analyzed the therapeutic effects of MT-1 CNS gene delivery in one of these LSD models. Constitutive expression of MT-1 exerted favorable phenotypic effects in both LSD models. MT-LSD mice showed a 5% to 10% increase in survival and slower disease progression as compared to not-transgenic LSD mice. Rescue of Purkinje cells from degeneration and apoptosis was also observed in the MT-LSD models. This phenotypic amelioration was accompanied by a modulation of the disease-associated activated inflammatory microglia phenotype, and by a reduction of oxidative stress. Importantly, for the clinical translation of these findings, the very same effects were obtained when MTs were delivered to brains by systemic AAV gene transfer. The authors concluded that MTs can be considered novel therapeutic agents (and targets) in LSDs and potentiate the effects of approaches aiming at correction of the disease-causing enzyme deficiency in the CNS.

Substrate Deprivation Therapy

Derrick-Roberts and colleagues (2017) stated that MPS I is the most common form of the MPS group of genetic diseases; it results from a deficiency in the lysosomal enzyme α-L-iduronidase, leading to accumulation of un-degraded heparan and dermatan sulphate glycosaminoglycan (GAG) chains in patient cells. Children with MPS suffer from multiple organ failure and die in their teens to early 20s. In particular, MPS I children also suffer from profound mental retardation and skeletal disease that restricts growth and movement. Neither neurological nor skeletal disease is adequately treated by
current therapy approaches. To overcome these barriers to effective therapy these researchers have developed and tested a treatment called substrate deprivation therapy (SDT). MPS I knockout mice were treated with weekly intravenous injections of 1 mg/kg rhodamine B for 6 months to assess the efficacy of SDT. Mice were assessed using biochemistry, micro-CT and a battery of behavioral tests to determine the outcome of treatment. A reduction in female body-weight gain was observed with the treatment as well as a decrease in lung GAG. Behavioral studies showed slight improvements in inverted grid and significant improvements in learning ability for female MPS I mice treated with rhodamine B. Skeletal disease also improved with a reduction in bone mineral volume observed. The authors concluded that rhodamine B is safe to administer to MPS I knockout mice where it had an effect on improving aspects of neurological and skeletal disease symptoms and may therefore provide a potential therapy or adjunct therapy for MPS I patients.

Enzyme Replacement Therapy (ERT) for Stroke Prevention in Fabry's Patients

Sheng and colleagues (2019) noted that Fabry's disease is the most prevalent lysosomal storage disorder and is notorious for its early multi-organ involvement leading to complications, including ischemic strokes and transient ischemic attacks (TIAs). Since 2001, ERT has become the mainstay treatment for Fabry's patients but the indications are not clearly defined. In a meta-analysis, these investigators reviewed the benefit of ERT for stroke prevention in Fabry's patients. They carried out a literature search from National Center for Biotechnology information (NCBI)/PubMed database without restriction of years for systematic review purposes. A systematic review of clinical cohort studies and trials was performed with pooled analysis of proportions. The pooled proportions and the CIs for stroke recurrence ratio were calculated for both ERT treatment group and native treatment groups. A total of 7 cohort studies and 2 RCTs involving 7,513 subjects (1,471 on
ERT versus 6,042 on native treatment) met inclusion criteria. The pooled proportions analysis showed that the stroke recurrence ratio in the ERT treatment group was 8.2% [95% CI: 0.038 to 0.126] and in native-treatment group was 16% [95% CI: 0.102 to 0.217]. Effect differences favored ERT treatment group over native treatment group (p = 0.03). The authors concluded that this meta-analysis based on the currently available data showed that ERT for Fabry's disease has beneficial effect on stroke prevention. Female carriers and atypically affected males could be started on ERT as soon as diagnosis is made. These researchers stated that further studies are needed to support the role of ERT in stroke prevention.

Appendix

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

<table>
<thead>
<tr>
<th>Hurler</th>
<th>Hurler-Scheie</th>
<th>Scheie</th>
</tr>
</thead>
</table>

Proprietary
- Severe developmental delay
- More progressive
- Severe respiratory disease
- Obstructive airway disease
- Death before age 10 years
- Little or no intellectual defect
- Respiratory disease
- Obstructive airway disease
- Cardiovascular disease
- Joint stiffness/contractures
- Skeletal abnormalities
- Decreased visual acuity
- Death in teens and 20's
- Normal intelligence
- Less progressive physical problems
- Corneal clouding
- Joint stiffness
- Valvular heart disease
- Death in later decades

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0028U</td>
<td>CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, copy number variants, common variants with reflex to targeted sequence analysis</td>
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<tr>
<td>96360</td>
<td>Intravenous infusion, hydration</td>
</tr>
<tr>
<td>96361</td>
<td></td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------</td>
</tr>
<tr>
<td>96365 -</td>
<td>Intravenous infusion, for therapy, prophylaxis, or</td>
</tr>
<tr>
<td>96368</td>
<td>diagnosis (specify substance or drug)</td>
</tr>
<tr>
<td>96379</td>
<td>Unlisted therapeutic, prophylactic, or diagnostic</td>
</tr>
<tr>
<td></td>
<td>intravenous or intra-arterial injection or infusion</td>
</tr>
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</table>

**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 |

Eliglustat (Cerdelga), Imiglucerase (Cerezyme), Miglustat (Zavesca) taliglucerase alfa (Elelyso) and Velaglucerase alfa (VPRIV):

No specific code for Eliglustat (Cerdelga), Miglustat (Zavesca) or VPRIV

**Other CPT codes related to the CPB:**


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-10 codes covered if selection criteria are met:

<p>| E75.22  | Gaucher's disease                                      |</p>
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<td>J1931</td>
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<td>E76.01</td>
<td>Mucopolysaccharosis, type I [Hurler's, Hurler-Scheie and Scheie's syndrome] [with moderate to severe symptoms]</td>
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<td>J0180</td>
<td>Injection, algalsidase beta, 1 mg</td>
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<td>E75.21</td>
<td>Fabry (-Anderson) disease</td>
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<td>E76.29</td>
<td>Other mucopolysaccharosis [MPS VI]</td>
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<td>E74.02</td>
<td>Pompe disease [infantile onset only]</td>
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<td>Injection, alglucosidase alfa, (lumizyme), 10 MG</td>
</tr>
<tr>
<td>E74.02</td>
<td>Pompe disease [Pompe disease]</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
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<td>---------</td>
<td>------------------</td>
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<td>Idursulfase (Elaprase):</td>
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<td>Implantation, revision or repositioning of tunneled intrathecal or epidural catheter, for long-term medication administration via an external pump or implantable reservoir/infusion pump</td>
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<tr>
<td>62351</td>
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<tr>
<td>62360 -</td>
<td>Implantation or replacement of device for intrathecal or epidural drug infusion</td>
</tr>
<tr>
<td>62362</td>
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</tr>
<tr>
<td>62365</td>
<td>Removal of subcutaneous reservoir or pump, previously implanted for intrathecal or epidural infusion</td>
</tr>
<tr>
<td>62367 -</td>
<td>Electronic analysis of programmable, implanted pump for intrathecal or epidural drug infusion (includes evaluation of reservoir status, alarm status, drug prescription status)</td>
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<tr>
<td>62370</td>
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<tr>
<td>95990 -</td>
<td>Refilling and maintenance of implantable pump or reservoir for drug delivery, spinal (intrathecal, epidural) or brain (intraventricular), includes electronic analysis of pump, when performed</td>
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<td><strong>Sebelipase alfa (Kanuma):</strong></td>
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<td>Other lipid storage disorders [Lysosomal acid lipase (LAL) enzyme deficiency]</td>
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<td><strong>Leukocyte and urinary glycosaminoglycan (uGAG) excretion:</strong></td>
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<td>Mucopolysaccharidoses</td>
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The above policy is based on the following references:


15. BioMarin Pharmaceuticals Inc. Naglazyme (galsulfase) solution for intravenous infusion only. Full Prescribing
Information. Novato, CA; BioMarin; revised March 2013.


33. Derrick-Roberts ALK, Jackson MR, Pyragius CE5, Byers S. Substrate deprivation therapy to reduce glycosaminoglycan synthesis improves aspects of neurological and skeletal pathology in MPS I mice. Diseases. 2017;5(1).


43. Erikson A, Forsberg H, Nilsson M, Astrom M, Mansson JE. Ten years’ experience of enzyme infusion therapy


70. Hughes D. Gaucher disease: Treatment. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed March 2015.


113. Pastores GM, Turkia HB, Gonzalez DE, et al. Development of anti-velaglucerase alfa antibodies in...
clinical trial-treated patients with Gaucher disease.

114. Patriot Pharmaceuticals, LLC. Miglustat. 
Prescribing Information. Horsham, PA: Patriot
Pharmaceuticals, LLC.; revised November 2017.

115. Pereira SJ, Berditchevsky CR, Marie SK. Report of the
first Brazilian infantile Pompe disease patient to be
treated with recombinant human acid alpha-

116. Pfizer Labs. Elelyso (taliglucerase alfa) for injection, for
intravenous use. Prescribing Information. New York,
NY: Pfizer, Inc; revised October 2019

Usefulness of alpha-glucosidase in Pompe disease
[summary]. Report IRR No.92. Buenos Aires, Argentina:
Institute for Clinical Effectiveness and Health Policy
(IECS); 2006.

Replacement enzyme therapy in Fabry’s disease
[summary]. Report IRR No. 20. Buenos Aires,
Argentina: Institute for Clinical Effectiveness and
Health Policy (IECS); 2004.

119. Pisani A, Bruzzese D, Sabbatini M, et al. Switch to
agalsidase alfa after shortage of agalsidase beta in
Fabry disease: A systematic review and meta-analysis

120. Platt FM, Jeyakumar M. Substrate reduction therapy.

bone disease to enzyme replacement therapy. Br J

enzyme replacement therapy for Pompe disease with
recombinant human alpha-glucosidase derived from
chinese hamster ovary cells. J Child Neurol. 2007;22


131. Shire PLC. Shire presents positive data for patients with type 1 Gaucher disease who switched to VPRIV. Also reported are results of retrospective analysis of phase I/II study, showing success in reaching therapeutic goals within 4 years of initiation of treatment. Shire News. Cambridge, MA: Shire; March 25, 2010.


146. U.S. Food and Drug Administration (FDA). FDA expands approval of drug to treat Pompe disease to patients of all ages; removes risk mitigation strategy requirements. FDA News Release. Silver Spring, MD: FDA; August 1, 2014.


150. Ultragenyx Pharmaceutical Inc. Mepsevii (vestronidase alfa-vjbk) injection, for intravenous use. Prescribing


155. van der Beek NA, Hagemans ML, van der Ploeg AT, et al. Pompe disease (glycogen storage disease type II): Clinical features and enzyme replacement therapy. Acta Neurol Belg. 2006;106(2):82-86.


Amendment to
Aetna Clinical Policy Bulletin Number: 0442 Lysosomal Storage Disorder Treatments

For the Pennsylvania Medical Assistance plan, the following drugs defer to the Statewide Preferred Drug List and related criteria (Enzyme Replacements, Gaucher Disease):

- Eliglustat (Cerdela)
- Imiglucerase (Cerezyme), Taliglucerase alfa (Elelyso), and Velaglucerase alfa (VPRIV)
- Miglustat (Zavesca)

For the Pennsylvania Medical Assistance plan, continued use of cerliponase alpha is considered medically necessary when the member continues to experience clinical benefit from cerliponase based on documentation of the degree of progression and the prescriber’s clinical judgment.

For the Pennsylvania Medical Assistance plan, vestronidase may be used in all age groups for which it has FDA approval.

For the Pennsylvania Medical Assistance plan, Hematopoietic Stem Cell Therapy is not considered to be experimental and investigational for treatment of Hurler syndrome in members under the approximate age of 2 years.

For the Pennsylvania Medical Assistance plan, the following criterion does not apply for vestronidase alfa-vjbk (Mepsevii): Elevated urinary glycosaminoglycan (uGAG) excretion at a minimum of 2-fold over the mean normal for age at initiation.