

Corporate Medical Policy

Enzyme Replacement Therapy (ERT) for Lysosomal Storage Disorders

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Description of Procedure or Service

Gaucher Disease

Gaucher disease (GD) is an inborn error of metabolism that affects the recycling of cellular glycolipids. It results from deficiency of a lysosomal enzyme glucocerebrosidase (also known as glucosylceramide or acid beta-glucosidase, GBA). Glucosylceramide (also called glucocerebroside) and several related compounds that ordinarily are degraded to glucose and lipid components by glucocerebrosidase accumulate within the lysosomes of cells in patients with GD. The decision to offer enzyme-replacement therapy (ERT) in patients with nonneuronopathic Gaucher disease (GD) (type 1 GD, GD1) is based upon disease severity, as determined by the initial assessment, or significant disease progression, as demonstrated through regular follow-up. ERT with a recombinant glucocerebrosidase (imiglucerase/Cerezyme®, velaglucerase alfa/VPRIV®, or taliglucerase alpha/Elelyso™); (the latter is not approved for use in the European Union) is the preferred treatment for patients with clinically significant manifestations of nonneuronopathic GD (GD1).

Clinical trials conducted in the late 1980s and early 1990s demonstrated the efficacy of ERT in patients with GD1 who were treated with glucocerebrosidase prepared from human placenta. The advance that was critical to the success of this technique was molecular targeting of the enzyme to tissue macrophages via mannose receptors expressed by these cells. A recombinant preparation has been available since 1993.

Lysosomal Acid Lipase (LAL) Deficiency

Patients with Lysosomal Acid Lipase (LAL) deficiency (also known as Wolman disease and cholesteryl ester storage disease [CESD]) have no or little LAL enzyme activity. This results in a build-up of fats within the cells of various tissues that can lead to liver and cardiovascular disease and other complications. Wolman disease often presents during infancy (around 2 to 4 months of age) and is a rapidly progressive disease. Patients with Wolman disease rarely survive beyond the first year of life. CESD is a milder, later-onset form of LAL deficiency and presents in early childhood or later. Life expectancy of patients with CESD depends on the severity of the disease and associated complications. Wolman disease affects one to two infants per million births, and CESD affects 25 individuals per million births.

The FDA granted Kanuma orphan drug designation because it treats a rare disease affecting fewer than 200,000 patients in the United States. Orphan drug designation provides financial incentives for rare disease drug development such as clinical trial tax credits, user fee waivers, and eligibility for market exclusivity to promote rare disease drug development. Kanuma was also granted breakthrough therapy designation as it is the first and only treatment available for Wolman disease, the very severe infant form of the disease. The breakthrough therapy designation program encourages the FDA to work collaboratively with sponsors, by providing

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timely advice and interactive communications, to help expedite the development and review of important new drugs for serious or life-threatening conditions. The Kanuma application was also granted a priority review, which is granted to drug applications that show a significant improvement in safety or effectiveness in the treatment of a serious condition. The manufacturer of Kanuma was granted a rare pediatric disease priority review voucher. This is a provision intended to encourage development of new drugs and biologics for the prevention and treatment of rare pediatric diseases.

Fabry Disease

Fabry disease is an inherited and often life-threatening disorder characterized by the progressive build-up of a substance known as GL-3 within the cells. It is an X-linked genetic disorder of glycosphingolipid metabolism. Deficiency of the lysosomal enzyme α -galactosidase A leads to progressive accumulation of glycosphingolipids, predominately GL-3, in many body tissues, starting early in life and continuing over decades. Clinical manifestations of Fabry disease include renal failure, cardiomyopathy, and cerebrovascular accidents. Accumulation of GL-3 in renal endothelial cells may also play a role in renal failure.

In April, 2003 the U.S Food and Drug Administration granted marketing approval for Fabrazyme (agalsidase beta) to be used to treat patients with Fabry disease. Fabrazyme lowers the amount of a substance called globotriaosylceramide (GL-3), which builds up in cells lining the blood vessels of the kidney and certain other cells. The lowering of GL-3 suggests that Fabrazyme may improve how Fabry disease affects the body; however a relationship of lower GL-3 to specific signs and symptoms of Fabry disease has not been proven.

Pompe Disease

Pompe disease is an inherited neuromuscular disorder caused by a defective gene that results in a deficiency of the enzyme acid alfa glucosidase (GAA). Without the GAA enzyme glycogen (a complex form of sugar) builds up in the cells of muscles throughout the body. This build-up of glycogen damages the cells, which can lead to deterioration of muscle function along with difficulties in movement and breathing. Pompe disease is progressive in that it worsens over time, as glycogen accumulates and causes more damage.

The symptoms of Pompe disease vary from person to person; they can emerge very slowly and at any age, so it is possible for someone to have it even if they are not experiencing any apparent problems. In addition, symptoms can be similar to those of other more common disorders, which may lead to a delay in correctly diagnosing the disease. If the disease is suspected, the diagnosis can be confirmed with a test called an enzyme assay, which measures the activity of the GAA enzyme in the patient's body. This activity is always lower than normal in people with Pompe disease.

In May, 2010 the U.S. Food and Drug Administration granted approval for Lumizyme for Late-Onset Pompe Disease in patients 8 years and older. In August, 2014, the FDA granted approval of Lumizyme to treat Pompe disease in treatment of patients with infantile-onset, including patients who are less than 8 years of age; therefore expanding approval to patients of all ages.

Mucopolysaccharidosis disorders:

- **Mucopolysaccharidosis I (MPS I)**

Mucopolysaccharidosis I (MPS I), an inherited, often life-threatening lysosomal disorder caused by a deficiency of the lysosomal enzyme, alpha-L-iduronidase. The

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deficiency of α -L-iduronidase, a lysosomal hydrolase which catalyzes the hydrolysis of terminal α -L-iduronic acid residues of dermatan sulfate and heparan sulfate. Reduced or absent α -L-iduronidase activity results in the accumulation of the GAG substrates, dermatan sulfate and heparan sulfate, throughout the body and leads to widespread cellular, tissue, and organ dysfunction. The rationale of Aldurazyme therapy in MPS I is to provide exogenous enzyme for uptake into lysosomes and increase the catabolism of GAG.

In April 2003, Aldurazyme received marketing approval from the U.S. Food and Drug Administration making it the first specific therapy for the treatment of this progressive and debilitating disease. Shortly thereafter, in June 2003, the European Commission granted marketing authorization for Aldurazyme in the European Union. Aldurazyme has been designated orphan drug status in both the United States and the European Union. Aldurazyme has since been approved in numerous other countries around the world.

- **Hunter Syndrome**

Hunter Syndrome (mucopolysaccharidosis II (MPS II)) is an X-linked recessive disease caused by insufficient levels of the lysosomal enzyme iduronate-2-sulfatase. This enzyme cleaves the terminal 2-O-sulfate moieties from the glycosaminoglycans (GAG) dermatan sulfate and heparan sulfate. Due to the missing or defective iduronate-2-sulfatase enzyme in patients with Hunter syndrome, GAG progressively accumulate in the lysosomes of a variety of cells, leading to cellular engorgement, organomegaly, tissue destruction, and organ system dysfunction.

In July, 2006, the U.S Food and Drug Administration granted approval for Elaprase (idursulfase) for the treatment of Hunter syndrome, also known as Mycopolysaccharidosis II (MPS II). It is the first and currently only treatment approved for Hunter syndrome.

- **Maroteaux-Lamy Syndrome**

Maroteaux-Lamy syndrome (mucopolysaccharidosis type VI; MPS VI) is a rare genetic disorder characterized by complete or partial lack of activity of the enzyme arylsulfatase B (also called N-acetylgalactosamine-4-sulfatase). Deficiency or absence of this enzyme activity leads to the accumulation of complex carbohydrates called glycosaminoglycans (previously known as mucopolysaccharides) in the body. The mucopolysaccharidoses (MPS) are a group of inherited lysosomal storage disorders. Abnormal accumulation of mucopolysaccharides leads to progressive involvement of multiple organ systems. The symptoms and severity of Maroteaux-Lamy syndrome can vary dramatically from one person to another; some individuals only develop mild symptoms, while others develop severe, even life-threatening complications. Common symptoms can include coarse facial features, corneal clouding, joint abnormalities, various skeletal malformations, an abnormally enlarged liver and/or spleen (hepatosplenomegaly), and hearing loss. Cardiac disease and restrictive pulmonary disease can also occur. Intelligence is usually not affected.

In 2005, the U.S. Food and Drug Administration (FDA) approved the enzyme replacement therapy known as Naglazyme® for the treatment of Maroteaux-Lamy syndrome. Maroteaux-Lamy syndrome occurs due to mutations in the ARSB gene and is inherited as an autosomal recessive disorder.

- **Sly Syndrome**

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Sly syndrome (mucopolysaccharidosis VII; MPS VII) is an inherited rare lysosomal disorder caused by mutations in the gene encoding beta-glucuronidase (GUSB). This genetic mutation leads to deficiency in the GUSB enzyme, which results in accumulation of GAG, a mucopolysaccharide, in cells throughout the body and can lead to multisystem tissue and organ damage. While symptoms can vary, most patients have skeletal abnormalities that progress with age and patients with the disease can also develop heart valve abnormalities, narrowed airways, and enlarged spleen and liver. Symptom severity is indicative of life expectancy, and while some patients do not survive beyond infancy, others may live into adolescence or adulthood.

In 2017, the FDA approved the enzyme replacement therapy known as Mepsevii™ for the treatment of Sly Syndrome (mucopolysaccharidosis type VII; MPS VII). Mepsevii is a recombinant human lysosomal beta glucuronidase and is the first FDA approved treatment for this condition.

- **Morquio A Syndrome**

Morquio A Syndrome (mucopolysaccharidosis Type IVA; MPS IVA) is a rare lysosomal storage disease characterized by deficient activity of the lysosomal enzyme N-acetylgalactosamine 6-sulfatase (GALNS). Without the activity of GALNS, the glycosaminoglycans dermatan sulfate and chondroitin-6 sulfate are not degraded and accumulate within the cell lysosome. This accumulation can lead to dysfunction in bodily tissues and organs. The first signs and symptoms of Morquio A syndrome usually become apparent during early childhood with affected individuals developing various skeletal abnormalities, including short stature, knock knees, and abnormalities of the ribs, chest, spine, hips, and wrists. Individuals with Morquio A syndrome tend to have joints that are loose and very flexible (hypermobility), but may also have restricted movement in certain joints. A characteristic feature of this disease is underdevelopment (hypoplasia) of a peg-like bone in the neck called odontoid process, which can lead to misalignment of the cervical vertebrae. This misalignment may then compress and damage the spinal cord, resulting in paralysis or death.

Additional symptoms of Morquio A syndrome is a cloudiness of the eye, specifically the cornea, leading to vision loss, along with hearing loss due to recurrent ear infections. Some individuals may have narrowing of the airway, leading to frequent upper respiratory infections and sleep apnea. Other common features include mildly “course” facial features, thin tooth enamel, heart valve abnormalities, and hepatosplenomegaly. Cognitive impairment is not generally associated with this disease. Individuals with rapidly progressing phenotype generally do not survive past the age of 30 and even those with a more slowly progressing disease course rarely survive beyond age 60 years. Spinal cord compression and airway obstruction are the major causes of death.

The U.S. Food and Drug Administration approved Vimizim, in February 2014 as the first and only therapy designed to treat Morquio A syndrome at the cellular level.

Batten Disease

Batten disease, also known as CLN2 disease is one of a group of disorders known as neuronal ceroid lipofuscinoses (NCLs). CLN2 disease is a rare inherited disorder that primarily affects the nervous system. In the late infantile form of the disease, signs and symptoms typically begin between ages 2 and 4 years. The initial symptoms can include language delay, recurrent seizures (epilepsy) and difficulty coordinating movements (ataxia). Affected children also develop muscle twitches (myoclonus) and vision loss. CLN2 disease affects essential motor skills, such as sitting and walking. Individuals with this disease often require the use of a wheelchair by late childhood and typically do not survive past their teen years. Batten disease

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is relatively rare, occurring in an estimated two to four of every 100,000 live births in the United States.

In April, 2017, the U.S Food and Drug Administration approved Brineura (cerliponase alfa) as a treatment for Batten disease. Brineura is the first FDA-approved treatment to slow loss of walking ability 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.

Related Policies:
Place of Service for Medical Infusion

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

BCBSNC will provide coverage for enzyme replacement therapy for lysosomal storage disorders when the medical necessity criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Enzyme Replacement Therapy for Lysosomal Storage Disorders is covered

Gaucher Disease Treatment:

Imiglucerase (Cerezyme®), Taliglucerase alfa (Elelyso™), and Velaglucerase Alfa (VPRIV®) may be considered medically necessary for treatment of Gaucher Disease when the following medical criteria are met:

Cerezyme® (imiglucerase for injection) may be considered medically necessary for long-term enzyme replacement therapy for pediatric (between 2 and 16 years of age) and adult patients with:

1. A confirmed diagnosis of Type 1 Gaucher disease [documentation of laboratory test results required];
 - a. Biochemical assay of beta-glucocerebrosidase activity (in leukocytes or skin fibroblasts) of less than 30% of normal values; or
 - b. Deoxyribonucleic acid (dna) testing (mutations in the glucocerebrosidase gene); **AND**
2. One or more of the following conditions:
 - a. Anemia
 - b. Thrombocytopenia
 - c. Bone disease
 - d. Hepatomegaly or splenomegaly

VPRIV® (velaglucerase alfa for injection) or **Elelyso™ (taliglucerase alfa for injection)** may be considered medically necessary for long-term enzyme replacement therapy (ERT) for pediatric (4 years of age and older) and adult patients with:

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1. A confirmed diagnosis of Type 1 Gaucher disease [documentation of laboratory test results required];
 - a. Biochemical assay of beta-glucocerebrosidase activity (in leukocytes or skin fibroblasts) of less than 30% of normal values; OR
 - b. Deoxyribonucleic acid (DNA) testing (mutations in the glucocerebrosidase gene); **AND**
2. The patient exhibits clinical signs and symptoms of Gaucher disease type 1 as demonstrated by two of the following:
 - a. Hematologic abnormalities including anemia and thrombocytopenia;
 - b. Clinically significant hepatomegaly;
 - c. Clinically significant splenomegaly;
 - d. Radiologic evidence of skeletal disease

Lysosomal Acid Lipase (LAL) Deficiency Treatment:

Kanuma (sebelipase alfa) may be considered medically necessary for the treatment of Lysosomal Acid Lipase (LAL) deficiency in pediatric patients aged 1 month and older and adult patients who have a diagnosis of lysosomal acid lipase deficiency (LAL-D) when the diagnosis is confirmed by:

1. A biochemical assay of lysosomal acid lipase (LAL) demonstrating deficient activity (in leukocytes or fibroblasts) per laboratory references; OR
2. Deoxyribonucleic acid (DNA) testing demonstrating biallelic pathogenic variants in *LIPA*

Continued therapy with Kanuma (sebelipase alfa) will be approved every 12 months based on treatment response and absence of intolerable adverse effects.

Fabry Disease

Fabrazyme (agalsidase beta) may be considered medically necessary for the treatment of Fabry disease when the following criteria are also met:

1. Fabrazyme will not be used concomitantly with other enzyme replacement or drugs to treat Fabry disease; **AND**
2. Receipt of any requests for alternative drugs to treat Fabry disease (e.g. Galafold) will result in closure of the Fabrazyme authorization.

Pompe Disease

Lumizyme (alglucosidase alfa) may be considered medically necessary for the treatment of Pompe disease, when the diagnosis is confirmed by:

1. An enzyme assay measuring the activity of GAA enzyme in the patient's body.

Mucopolysaccharidosis Disorder Treatments:

Aldurazyme (laronidase) may be considered medically necessary for treatment in patients with Mucopolysaccharidosis type I (MPSI), diagnosed with:

1. Hurler and Hurler-Scheie forms of Mucopolysaccharidosis I (MPS I); OR
2. Scheie form of Mucopolysaccharidosis I (MPS I) with moderate to severe symptoms.

Because of the potential for infusion reactions, patients should receive antihistamines with or without antipyretics prior to infusion.

Elaprased (idursulfase) may be considered medically necessary for patient 5 years of age and older, diagnosed with Mucopolysaccharidosis II (MPS II; Hunter Syndrome).

The safety and efficacy of Elaprased have not been established in pediatric patients less than 16 months of age

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Mepsevii (vestronidase alfa-vjkk) may be considered medically necessary for treatment of pediatric and adult patients with Mucopolysaccharidosis VII (MPS VII; Sly Syndrome) when the diagnosis is confirmed by:

1. Leukocyte or fibroblast glucuronidase enzyme assay or genetic testing; AND
2. Elevated urinary glycosaminoglycan (uGAG) excretion at a minimum of 2-fold over the mean normal for age at start of therapy.

Because of the potential for infusion reactions, patients should receive antihistamines with or without antipyretics prior to infusion.

Naglazyme (galsulfase) may be considered medically necessary for patients with Mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy Syndrome) when the diagnosis is confirmed by:

1. A biochemical assay of N-acetylgalactosamine 4-sulfatase (arylsulfatase B, ASB) demonstrating deficient activity (in leukocytes or fibroblasts) per laboratory references; AND
 - a. Multiple sulfatase deficiencies have been ruled out (via assay of a second sulfatase); AND
 - b. If fibroblasts are used, I-cell disease has been ruled out; OR
2. Deoxyribonucleic acid (DNA) testing (MUTATIONS IN THE ARSB GENE).

Because of the potential for infusion reactions, patients should receive antihistamines with or without antipyretics prior to infusion.

Vimizim (elosulfase alfa) may be considered medically necessary for patients 5 years of age and older, with Mucopolysaccharidosis IVA (MPS IVA; Morquio A Syndrome) when the diagnosis is confirmed by:

1. Reduced N-acetylgalactosamine 6-sulfatase (GALNS) enzyme activity; OR
2. Identification of biallelic variants in GALNS upon genetic testing

Continued therapy with Vimizim (elosulfase alfa) will be approved beyond 6 months based on demonstration of ongoing effectiveness and absence of intolerable adverse effects.

Because of the potential for infusion reactions, patients should receive antihistamines with or without antipyretics prior to infusion.

Batten Disease (CLN2)

Brineura (cerliponase alfa) may be considered medically necessary for patients 3 years of age or older confirmed by the following:

1. Deficiency of tripeptidyl peptidase 1 (TPP1) enzyme

Consultation with a neurologist is required prior to initiating therapy with Brineura

****MEDICAL RECORDS DOCUMENTING THE MEMBER'S CONDITION AS WELL AS LABORATORY RESULTS CONFIRMING LYOSOMAL STORAGE DISORDERS ARE REQUIRED WITH THE PRIOR APPROVAL REQUEST.****

When Enzyme Replacement Therapy for Lysosomal Storage Disorders is not covered

Enzyme Replacement Therapy for Lysosomal Storage Disorders is considered **investigational** for any other indication not listed above.

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Policy Guidelines

Cerezyme® (imiglucerase)

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

VPRIV® (velaglucerase alfa)

VPRIV should be administered under the supervision of a healthcare professional. The recommended starting VPRIV dosage in naïve adults and naïve pediatric patients 4 years of age and older is 60 Units/kg administered every other week as a 60-minute intravenous infusion. The dosage can be adjusted based on achievement and maintenance of each patient's therapeutic goals. Adults and pediatric patients 4 years of age and older currently being treated on a stable dosage of imiglucerase for type 1 Gaucher disease may be switched to VPRIV by starting treatment with VPRIV at the previous imiglucerase dosage two weeks after the last imiglucerase dose. VPRIV should be administered under the supervision of a healthcare professional as a 60-minute intravenous infusion. The dosage can be adjusted based on achievement and maintenance of each patient's therapeutic goals.

Elelyso™ (taliglucerase alfa)

The recommended dosage of Elelyso for treatment-naïve adult and pediatric patients 4 years of age and older is 60 units per kg of body weight administered every other week as a 60 to 120 minute intravenous infusion. Dosage adjustments can be made based on achievement and maintenance of each patient's therapeutic goals. Elelyso should be reconstituted, diluted, and administered under the supervision of a healthcare professional.

Note: Patients can be switched between imiglucerase and taliglucerase. Initiate taliglucerase alfa using the patient's same previous imiglucerase dose and administer every 2 weeks. Conversion to taliglucerase alfa is based on a single study of patients stabilized on a biweekly imiglucerase dose for ≥ 6 months.

Kanuma (sebelipase alfa)

Kanuma (sebelipase alfa) is a hydrolytic lysosomal cholesteryl ester and triacylglycerol-specific enzyme indicated for the treatment of patients with a diagnosis of Lysosomal Acid Lipase (LAL) deficiency. 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, the dose can be increased 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.

Fabrazyme (agalsidase beta)

Fabrazyme (agalsidase beta) is a) is a recombinant human α -galactosidase A enzyme indicated for the treatment of patient with Fabry disease. The recommended dosage is 1mg/kg of body weight given every two weeks as an intravenous (IV) infusion. Fabrazyme is available as 35mg or 5mg single-use vials as lyophilized powder for reconstitution with Sterile Water for injection to yield 5mg/ml. Patients should receive antipyretics prior to infusion.

The initial IV infusion rate should be no more than 0.25 mg/min (15 mg/hr). The infusion rate may be slowed in the event of infusion reactions. After patient tolerance to the infusion is well

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established, the infusion rate may be increased in increments of 0.05 to 0.08 mg/min (increments of 3 to 5 mg/hr) with each subsequent infusion. For patients weighing < 30 kg, the maximum infusion rate should remain at 0.25 mg/min (15 mg/hr). For patients weighing ≥ 30 kg, the administration duration should not be less than 1.5 hours (based on individual patient tolerability). Fabrazyme is for single-use only and pretreatment with antihistamines with or without antipyretics is recommended 30 to 60 minutes prior to the start of infusion.

Lumizyme (alglucosidase alfa)

Lumizyme (alglucosidase alfa) is a hydrolytic lysosomal glycogen-specific enzyme indicated for treatment of Pompe disease (GAA deficiency). Recommended dosage is 20mg per kg body weight administered every 2 weeks as an intravenous (IV) infusion. Infusions should be administered in a step-wise manner with the initial infusion rate no more than 1mg/kg/hr. The rate may be increased by 2mg/kg/hr every 30 minutes once tolerance has been established, until a maximum rate of 7mg/kg/hr is reached. Total administration time is 4 hours.

Lumizyme (alglucosidase) should be reconstituted, diluted and administered by a healthcare professional, and is for single-use only. Pretreatment with antihistamines with or without antipyretics is recommended 30 to 60 minutes prior to the start of infusion.

Aldurazyme (laronidase)

Aldurazyme (laronidase) is a hydrolytic lysosomal glycosaminoglycan (GAG)- specific enzyme indicated for patients with Hurler and Hurler-Scheie forms of Mucopolysaccharidosis I (MPS I) and for patients with the Scheie form who have moderate to severe symptoms. The risks and benefits of treating mildly affected patients with the Scheie form have not been established. Aldurazyme is administered under the supervision of a healthcare professional with recommended dosage regimen 0.58 mg per kg of body weight administered once weekly as an intravenous (IV) infusion. Pretreatment with antihistamines with or without antipyretics is recommended 30 to 60 minutes prior to the start of infusion.

Each vial of Aldurazyme provides 2.9 milligrams (mg) of laronidase in 5.0 milliliters (mL) of solution and is intended for single use only. The concentrated solution for infusion must be diluted with 0.9% Sodium Chloride Injection to a final volume of 100 mL or 250 mL, using aseptic techniques. The final volume of the infusion is determined by the patient's body weight. Patients with a body weight of 20 kg or less should receive a total volume of 100 mL. Patients with a body weight greater than 20 kg should receive a total volume of 250 mL.

The entire infusion volume (100 mL for patients weighing 20 kg or less and 250 mL for patients weighing greater than 20 kg) should be delivered over approximately 3 to 4 hours. The initial infusion rate of 10 µg/kg/hr may be incrementally increased every 15 minutes during the first hour, as tolerated, until a maximum infusion rate of 200 µg/kg/hr is reached. The maximum rate is then maintained for the remainder of the infusion (2-3 hours)

Elaprase (idursulfase)

Elaprase (idursulfase) is a hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme indicated for patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II). Elaprase is administered under the supervision of a healthcare professional with recommended dosage regimen 0.5 mg per kg of body weight administered once weekly as an intravenous (IV) infusion. Pretreatment with antihistamines with or without antipyretics is recommended 30 to 60 minutes prior to the start of infusion. The total volume of infusion should be administered over a period of 3 hours with gradual decrease to 1 hour if no hypersensitivity reactions observed, not to exceed 8 hours. Elaprase is provided in 6mg/3ml (2mg/ml) of single-use vials.

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In patients 16 months to 5 years of age, no data are available to demonstrate improvement in disease-related symptoms or long term clinical outcome; however, treatment with Elaprase has reduced spleen volume similarly to that of adults and children 5 years of age and older. The safety and efficacy of Elaprase have not been established in pediatric patients less than 16 months of age.

Mepsevii (vestronidase alfa-vjkb)

Mepsevii (vestronidase alfa-vjkb) is a recombinant form of human beta glucuronidase. It is indicated for patients with Mycopolysaccharidosis VII (MPS VII; Sly Syndrome) and is intended to provide exogenous glucuronidase enzyme for uptake into cellular lysosomes. Mepsevii is administered under the supervision of a healthcare professional with recommended dosage regimen of 4mg per kg of body weight administered once every two weeks as an intravenous infusion. Pretreatment with non-sedating antihistamines with or without antipyretics is recommended 30 to 60 minutes prior to the start of infusion. The total volume of infusion should be delivered over approximately 4 hours and 2.5% of the total volume should be initially infused over the first hour with infusion rate increased as tolerated to complete the remaining infusion over the following 3 hours per specific dosing guidelines.

Naglazyme (galsulfase)

Naglazyme (galsulfase) is a recombinant form of N-acetylgalactosamine 4-sulfatase, produced in Chinese hamster cells. It is a hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme indicated for patients with Mycopolysaccharidosis IV (MPS IV; Maroteaux-Lamy Syndrome). Naglazyme is administered under the supervision of a healthcare professional with recommended dosage regimen of 1mg per kg of body weight administered once weekly as an intravenous infusion. Pretreatment with antihistamines with or without antipyretics is recommended 30 to 60 minutes prior to the start of infusion. The total volume of infusion should be delivered over a period of time of no less than 4 hours and diluted with 0.9% Sodium Chloride for a final volume of 250mg and delivered using an infusion pump. The initial infusion rate should be 6 mL per hour for the first hour. If the infusion is well tolerated, the rate may be increased to 80mL per hour for the first hour for the remaining 3 hours, The infusion time can be extended up to 20 hours if infusion reactions occur. Each vial of NAGLAZYME provides 5 mg of galsulfase (expressed as protein content) in 5 mL of solution and is intended for single use only.

Naglazyme has been shown to improve walking and stair-climbing capacity.

Vimizim (elosulfase alfa)

Vimizim (elosulfase alfa) is a hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme indicated for patients with a diagnosis of Morquio A Syndrome (mucopolysaccharidosis Type IVA; MPS IVA). Vimizim is administered under the supervision of a healthcare professional with recommended dosage regimen of 2mg per kg of body weight administered once weekly as an intravenous infusion, over a minimum range of 3.5 to 4.5 hours based on infusion volume. Pretreatment with antihistamines with or without antipyretics is recommended 30 to 60 minutes prior to the start of infusion. The total volume of infusion should be delivered over a minimum of 4.5 hours and diluted in 0.9% Sodium Chloride for a final volume of 100mL or 250mL.

For patients who weigh less than 25kg, the initial infusion rate should be 3 mL per hour for the first 15minutes and, if tolerated, increased to 6 mL per hour for the next 15 minutes, not to exceed 36 mL per hour and delivered over a minimum of 3.5 hours. The initial infusion rate for patients who weighs 25kg or more, should be 6 mL per hour for the first 15 minutes. If the infusion is well tolerated, then the rate may be increased to 12 mL per hour for the next 15 minutes, not to exceed 72 mL per hour and delivered over a minimum of 4.6 hours. Each vial of Vimizim provides 5mg/5mL and intended for single use only.

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Safety and effectiveness of Vimizim have not been established in individuals less than 5 years of age.

Brineura (cerliponase alfa)

Brineura is an enzyme replacement therapy. The active ingredient (cerliponase alfa) is a recombinant form of human TPP1, the enzyme deficient in patients with CLN2 disease. Brineura is administered into the cerebrospinal fluid (CSF) by infusion via a specific surgically implanted reservoir and catheter in the head (intraventricular access device). Brineura must be administered under sterile conditions to reduce the risk of infections, and treatment should be managed by a health care professional knowledgeable in intraventricular administration. The recommended dose in pediatric patients 3 years of age and older is 300mg administered once every other week by intraventricular infusion, followed by an infusion of electrolytes. The complete Brineura infusion, including the required infusion of intraventricular electrolytes, lasts approximately 4.5 hours. Pre-treatment of patients with antihistamines with or without antipyretics or corticosteroids is recommended 30 to 60 minutes prior to initiating infusion. **Based on the administration methodology, Brineura may not be appropriate as a home infusion. The “Site of Care Eligibility” requirements below do not apply to Brineura.**

The efficacy of Brineura was established in a non-randomized, single-arm dose escalation clinical study in 22 symptomatic pediatric patients with CLN2 disease, and compared to 42 untreated patients with CLN2 disease from a natural history cohort (an independent historical control group) who were at least 3 years old and had motor or language symptoms. Taking into account age, baseline walking ability and genotype, Brineura-treated patients demonstrated fewer declines in walking ability compared to untreated patients in the natural history cohort.

The safety of Brineura was evaluated in 24 patients with CLN2 disease aged 3 to 8 years who received at least one dose of Brineura in clinical studies. The safety and effectiveness of Brineura have not been established in patients less than 3 years of age.

Enzyme Replacement Therapy (ERT) for Lysosomal Storage Disorders - Site of Care Eligibility

1. ERT administration may be given in an inpatient setting if the inpatient setting is medically necessary. An inpatient admission for the sole purpose of ERT infusion is not medically necessary.
2. ERT administration in a hospital outpatient setting is considered medically necessary if the following criteria are met:
 - a. History of mild adverse events that have not been successfully managed through mild pre-medication (diphenhydramine, acetaminophen, steroids, fluids, etc.), OR
 - b. Inability to physically and cognitively adhere to the treatment schedule and regimen complexity, OR
 - c. First infusion, OR
 - d. Less than 3 months since first ERT infusion, OR
 - e. First infusion after six months of no ERT infusions, OR
 - f. Requirement of a change in ERT product.
3. Members who do not meet the criteria above are appropriate for ERT administration in a **home-based** or physician office setting with or without supervision by a certified healthcare professional. Inpatient and hospital outpatient infusion, in the absence of the criteria in #1 or #2 above is considered not medically necessary.

Billing/Coding/Physician Documentation Information

Enzyme Replacement Therapy (ERT) for Lysosomal Storage Disorders

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: J0180, J0220, J0221, J0567, J1322, J1458, J1743, J1786, J1931, J2840, J3060, J3385, J3397, J3490, J3590, C9399

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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U.S. Food and Drug Administration (FDA). Naglazyme (galsulfase) Package Insert. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/125117_0000_lbl.pdf (Accessed August 25, 2016)

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National Institutes of Health (NIH), U.S. National Library of Medicine. Genetics Home Reference for Mycopolyaccharidosis type IV. Available at <https://ghr.nlm.nih.gov/condition/mucopolysaccharidosis-type-iv> (Accessed March 24, 2017).

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Medical Director review 8/2018

Specialty Matched Consultant Advisory Panel review 7/2019

Policy Implementation/Update Information

For Policy titled, “Enzyme Replacement Therapy for Gaucher Disease”

7/1/15 Original policy developed titled, “Enzyme Replacement Therapy for Gaucher Disease” with policy statement, “BCBSNC will provide coverage for enzyme replacement therapy for Gaucher disease when the medical necessity criteria and guidelines shown below are met.” Medical Director review 6/2015. Notification given 7/1/2015 for effective date 9/1/2015. (td)

For Policy titled, “Enzyme Replacement Therapy for Lysosomal Storage Disorders”

2/29/16 Policy name changed from “Enzyme Replacement Therapy for Lysosomal Storage Disorders” to “Enzyme Replacement Therapy for Lysosomal Storage Disorders”. Policy revised to include criteria and information regarding Kanuma. References updated. Senior Medical Director review 2/2016. (td)

5/31/16 Specialty Matched Consultant Advisory Panel review. Senior Medical Director review 3/2016. Coding updates only. (jd)

9/30/16 Policy revised to include criteria and information for Naglazyme for Maroteaux-Lamy Syndrome, and additional criteria added for Kanuma. Code J1458 added to coding section for Naglazyme (Galsulfase). Policy noticed 10/1/2016 for effective date 12/30/16. References updated. (jd)

12/30/16 Code section updated. (jd)

4/28/17 Added “ERT” to policy title. Formatting changes made. Policy revised to include criteria and guidelines for Vimizim for Morquio Type A Syndrome, as well as the following: Aldurazyme, Elapraxe, Fabrazyme, and Luminzyme for respective indications noted. Added Related Policy “Place of Service for Medical Infusions”. Policy Guidelines updated to include guidelines for added drugs, and guidelines for “**Site of Care Eligibility**” related to infusion. Codes J1322, J1931, J1743, J0180, J0220, J0221 added to coding section. Specialty Matched Consultant Advisory Panel review 3/2017. Medical Director review 3/2017. Notification given

Enzyme Replacement Therapy (ERT) for Lysosomal Storage Disorders

- 4/28/17 for policy effective 7/1/17. Codes J1322, J1743, J0180, and J0221 will be noticed 7/1/17, effective for PPA 10/1/17 (jd)
- 6/30/17 Policy revised to include description, medically necessary criteria and guidelines for Brineura for Batten disease (CLN2). Codes J3490, J3590 and C9399 added to policy. (jd)
- 12/29/17 References updated. Code C9014 added to coding section effective 1/1/18. (jd)
- 4/13/18 Specialty Matched Consultant Advisory Panel review 3/2018. Medical Director review 3/2018. (jd)
- 8/10/18 Policy revised to include medically necessary criteria and associated guideline information for Mepsevii for treatment of Mucopolysaccharidosis VII (MPS VII; Sly syndrome). Specialty Matched Consultant Advisory Panel review 7/26/2018. Policy noticed 8/10/2018 for effective date of 10/9/2018. References added. (krc)
- 9/7/18 Added the following to “When Covered” section for Fabrazyme: “1. Fabrazyme will not be used concomitantly with other enzyme replacement or drugs to treat Fabry disease; AND 2. Receipt of any requests for alternative drugs to treat Fabry disease (e.g. Galafold) will result in closure of the Fabrazyme authorization.” Medical Director review 8/2018. Policy remains on notice 8/10/2018 for effective date of 10/9/2018. (krc)
- 12/31/18 Added HCPCS codes J0567 and J3397 to Billing/Coding section and deleted code C9014 effective 1/1/19. (krc)
- 10/1/19 Specialty Matched Consultant Advisory Panel review 7/17/2019. No change to policy intent. (krc)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.