# Enzyme Replacement Therapy

## NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

## BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

## DESCRIPTION

The intent of the Enzyme Replacement Therapy policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines and clinical studies while steering utilization to the most cost-effective medication within the therapeutic class.

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy. All other indications are considered experimental/investigational and not medically necessary.

FDA-Approved Indications

1. **Aldurazyme (laronidase)** is indicated for adult and pediatric 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.
2. **Brineura (cerliponase alfa)** is indicated 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.
3. **Elaprase (idursulfase)** is indicated for patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II). Elaprase has been shown to improve walking capacity in patients 5 years and older. 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.

4. **Fabrazyme (agalsidase beta)** is indicated for adult and pediatric patients 2 years of age and older with Fabry disease. Fabrazyme reduces globotriaosylceramide (GL-3) deposition in capillary endothelium of the kidney and certain other cell types.
5. **Kanuma (sebelipase alfa)** is indicated for the treatment of patients with a diagnosis of Lysosomal Acid Lipase (LAL) deficiency.
6. **Lumizyme (alglucosidase alfa)** is indicated for patients with Pompe disease (acid alpha-glucosidase [GAA] deficiency).
7. **Nexviazyme (avalglucosidase alfa-ngpt)** is indicated for the treatment of late-onset Pompe disease (acid alpha-glucosidase [GAA] deficiency) in patients ≥ 1 year of age.
8. **Mepsevii (vestronidase alfa-vjbk)** is indicated in pediatric and adult patients for the treatment of mucopolysaccharidosis VII (MPS VII, Sly syndrome).
9. **Naglazyme (galsulfase)** is indicated for patients with mucopolysaccharidosis VI (MPS VI, Maroteaux-Lamy syndrome). Naglazyme has been shown to improve walking and stair-climbing capacity.
10. **Nulibry (fodenopterin)** is indicated to reduce the risk of mortality in patients with molybdenum cofactor deficiency (MoCD) Type A.
11. **Revcovi (elapegademase-lvlr)** is indicated for the treatment of adenosine deaminase severe combined immune deficiency (ADA-SCID) in pediatric and adult patients.
12. **Vimizim (elosulfase alfa)** is indicated for patients with Mucopolysaccharidosis type IVA (MPS IVA, Morquio A syndrome).
13. **Xenpozyme (olipudase alfa-rpcp)** is indicated for the treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) in adult and pediatric patients.

## POLICY

Required Documentation

Submission of the following information is necessary to initiate the prior authorization review:

**I. Aldurazyme (laronidase)**
- a. Initial requests: alpha-L-iduronidase enzyme assay or genetic testing results supporting diagnosis.
- b. Continuation requests: chart notes documenting a clinically positive response to therapy, which shall include improvement, stabilization, or slowing of disease progression.

**II. Brineura (cerliponase alfa)**
- a. Tripeptidyl peptidase 1 (TPP1) enzyme assay or genetic testing results supporting diagnosis
- b. Continuation requests: chart notes documenting a clinically positive response to therapy, which shall include improvement, stabilization, or slowing of disease progression.

**III. Elaprase (idursulfase)**
- a. Initial requests: Iduronate 2-sulfatase enzyme assay or genetic testing results supporting diagnosis
- b. Continuation requests: chart notes documenting a clinically positive response to therapy, which shall include improvement, stabilization, or slowing of disease progression.

**IV. Fabrazyme (agalsidase beta)**
- a. Initial requests: Alpha-galactosidase enzyme assay or genetic testing results supporting diagnosis. In the case of obligate carriers, the documentation must be submitted for the parent
- b. Continuation requests: lab results or chart notes documenting a positive response to therapy (e.g., reduction in plasma globotriaosylceramide [GL-3] or GL-3 inclusions, improvement and/or stabilization in renal function, pain reduction).

**V. Kanuma (sebelipase alfa)**
- a. Initial requests: Lysosomal acid lipase enzyme assay or genetic testing results supporting diagnosis

b. Continuation requests: lab values or chart notes documenting a positive response 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).

**VI. Lumizyme (alglucosidase alfa)**

a. Initial requests: Acid alpha-glucosidase enzyme assay or genetic testing results supporting diagnosis
b. Continuation requests: chart notes documenting a positive response 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).

**VII. Nexviazyme (alglucosidase alfa-ngpt)**

a. Initial requests: Acid alpha-glucosidase enzyme assay or genetic testing results supporting diagnosis
b. Continuation requests: chart notes documenting a positive response to therapy (e.g., improvement, stabilization, or slowing of disease progression for motor function, walking capacity, respiratory function, muscle strength).

**VIII. Nulibry (fodenopterin)**

a. Initial requests: genetic testing results documenting a mutation in the molybdenum cofactor synthesis gene 1 *(MOSC1)*.
b. Continuation requests:
    i. Genetic testing results documenting a mutation in the molybdenum cofactor synthesis gene 1 *(MOSC1)*.
    ii. Chart notes or medical records documenting a benefit from therapy (e.g., improvement, stabilization, or slowing of disease progression for encephalopathy, seizure activity, improved or normalized uric acid, urinary S-sulfocysteine, and xanthine levels).

**IX. Mepsevii (vestronidase alfa-vjbk)**

a. Initial requests: Beta-glucuronidase enzyme assay or genetic testing results supporting diagnosis
b. Continuation requests: chart notes documenting a clinically positive response to therapy, which shall include improvement, stabilization, or slowing of disease progression.

**X. Naglazyme (galsulfase)**

a. Initial requests: N-acetylgalactosamine 4-sulfatase (arylsulfatase B) enzyme assay or genetic testing results supporting diagnosis
b. Continuation requests: chart notes documenting a clinically positive response to therapy, which shall include improvement, stabilization, or slowing of disease progression.

**XI. Revcovi (elapegademase-lvlr)**

a. Initial requests: Enzyme assay or genetic testing results supporting diagnosis of ADA deficiency
b. Continuation requests: chart notes documenting a clinically positive response to therapy as evidenced by disease stability or disease improvement (e.g., normalization of plasma ADA activity, erythrocyte dATP levels, improvement of disease symptoms, etc.).

**XII. Vimizim (elosulfase alfa)**

a. Initial requests: N-acetylgalactosamine 6-sulfatase enzyme assay or genetic testing results supporting diagnosis
b. Continuation requests: chart notes documenting a clinically positive response to therapy, which shall include improvement, stabilization, or slowing of disease progression.

XIII. **Xenpozyme (olipudase alfa-rpcp)**

a. Initial requests:
    i. Molecular genetic testing confirming mutation in the sphingomyelin phosphodiesterase 1 (SMPD1) gene, or enzyme assay confirming absent or reduced function of acid sphingomyelinase (ASM) enzyme.
    ii. Chart notes or medical records documenting clinical presentation consistent with ASMD type A/B or ASMD type B

b. Continuation requests: Chart notes documenting a clinically positive response to therapy which may include improvement in pulmonary function, splenomegaly, hepatomegaly, or platelet count.

Criteria for Initial Approval

I. **Aldurazyme (laronidase)** is considered **medically necessary** for treatment of Mucopolysaccharidosis I (MPS I) when ALL the following criteria are met:
   a. Diagnosis of MPS I was confirmed by enzyme assay demonstrating a deficiency of alpha-L-iduronidase enzyme activity or by genetic testing.
   b. 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).

   **Approval** is for **12 months**

II. **Brineura (cerliponase alfa)** is considered **medically necessary** for slowing the loss of progression in symptomatic members with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) when ALL the following criteria are met:
   a. Diagnosis of CLN2 was confirmed by enzyme assay demonstrating a deficiency of tripeptidyl peptidase 1 (TPP1) enzyme activity or by genetic testing.
   b. Member is 3 years of age or older.
   c. Brineura will be administered by, or under the direction of a physician knowledgeable in intraventricular administration.
   d. Member does not have acute intraventricular access device-related complications (e.g., leakage, device failure, or device-related infection) or a ventriculoperitoneal shunt.
   e. Documentation of baseline motor function using the motor domain of CLN2 Clinical Rating Scale confirms the member is ambulatory at the time of treatment initiation.

   **Approval** is for **12 months**

III. **Elaprase (idursulfase)** is considered **medically necessary** for treatment of Mucopolysaccharidosis II (MPS II) when the following criteria is met:
   a. Diagnosis of MPS II was confirmed by enzyme assay demonstrating a deficiency of iduronate 2-sulfatase enzyme activity or by genetic testing.

   **Approval** is for **12 months**

IV. **Fabrazyme (agalsidase beta)** is considered **medically necessary** for treatment of Fabry disease when ALL the following criteria are met:
   a. 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. Fabrazyme will not be used in combination with Galafold.

   **Approval** is for **12 months**

V. **Kanuma (sebelipase alfa)** is considered **medically necessary** for treatment of Lysosomal Acid Lipase (LAL) deficiency when ALL the following criteria are met:
   a. Diagnosis of LAL deficiency was confirmed by enzyme assay demonstrating a deficiency of lysosomal acid lipase enzyme activity or by genetic testing.

b. Member has alanine aminotransferase level (ALT) ≥ 1.5 times the upper limit of normal (based on the age- and gender-specific normal ranges) on two consecutive ALT measurements obtained at least one week apart.

**Approval** is for **12 months**

VI. **Lumizyme (alglucosidase alfa)** is considered **medically necessary** for treatment of Pompe disease when the following criteria is met:
   a. Diagnosis of Pompe disease was confirmed by enzyme assay demonstrating a deficiency of acid alpha-glucosidase enzyme activity or by genetic testing.

**Approval** is for **12 months**

**VII. Nexviazyme (alglucosidase alfa-ngpt)** is considered **medically necessary** for treatment of Pompe disease when the following criteria is met:
   a. Diagnosis of Pompe disease was confirmed by enzyme assay demonstrating a deficiency of acid alpha-glucosidase enzyme activity or by genetic testing.
   b. Member is 1 year of age or older

**Approval** is for **12 months**

VIII. **Nulibry (fosdenopterin)** is considered **medically necessary** for treatment of molybdenum cofactor deficiency (MoCD) Type A. when the following criteria is met:
   a. Member has clinical signs and symptoms associated with MoCD Type A (e.g., encephalopathy, intractable seizures, developmental delay, decreased uric acid levels, elevated urinary S-sulfocysteine and/or xanthine levels).
   b. Member has a presumed diagnosis of MoCD Type A and genetic test results are pending

**Approval** is for **3 months**

**OR**
   a. Genetic testing results documenting a mutation in the molybdenum cofactor synthesis gene 1 *(MOSC1)*

**Approval** is for **12 months**

IX. **Mepsevii (vestronidase alfa-vjbk)** is considered **medically necessary** for treatment of mucopolysaccharidosis VII (MPS VII, Sly Syndrome) when ALL the following criteria are met:
   a. Diagnosis of MPS VII was confirmed by enzyme assay demonstrating a deficiency of beta-glucuronidase enzyme activity or by genetic testing.
   b. Elevated urinary glycosaminoglycan (uGAG) excretion at a minimum of 2-fold over the mean normal for age at initiation of treatment with Mepsevii.

**Approval** is for **12 months**

X. **Naglazyme (galsulfase)** is considered **medically necessary** for treatment of mucopolysaccharidosis VI (MPS VI, Maroteaux-Lamy syndrome) when the following criteria is met:
   a. 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.

**Approval** is for **12 months**

XI. **Revcovi (elapegademase-lvlr)** is considered **medically necessary** for treatment of severe combined immunodeficiency disease (SCID) associated with adenosine deaminase (ADA) deficiency when ALL the following criteria are met:
   a. The condition has failed to respond to a bone marrow transplant (BMT), or the member is not currently a suitable candidate for BMT.

   **Approval** is for **12 months**

XII. **Vimizim (elosulfase alfa)** is considered **medically necessary** for treatment of Mucopolysaccharidosis type IVA (MPS IVA, Morquio A syndrome) when the following criteria is met:
   a. Diagnosis of MPS IVA was confirmed by enzyme assay demonstrating a deficiency of N-acetylgalactosamine 6-sulfatase enzyme activity or by genetic testing.

   **Approval** is for **12 months**

XIII. **Xenpozyme (olipudase alfa-rpcp)** is considered **medically necessary** for the treatment of acid sphingomyelinase deficiency (ASMD) in adult and pediatric patients when the following criteria is met:
   a. Diagnosis of ASMD is confirmed by one of the following:
      i. Enzyme assay demonstrating reduced or absent activity (less than 10% of controls) of acid sphingomyelinase (ASM) enzyme in peripheral blood leukocytes, cultured skin fibroblasts, or dried blood spot (DBS); **OR**
      ii. Molecular genetic testing identifying biallelic pathogenic variants in sphingomyelin phosphodiesterase-1 (SMPD1)
   b. The member has a clinical presentation consistent with ASMD type A/B or ASMD type B
   c. The member is not being treated for CNS disease manifestations of ASMD
   d. The requested medication must be prescribed by, or in consultation with, a geneticist, hepatologist, gastroenterologist, or pulmonologist, or other specialist with expertise in the diagnosis and management of non-CNS disease manifestations of ASMD
   e. Dose does not exceed 3 mg/kg every 2 weeks

   **Approval** is for **12 months**

<u>Continuation of Therapy</u>

I. **Aldurazyme (laronidase)** is considered **medically necessary** for continuation of treatment of Mucopolysaccharidosis I (MPS I) in members who are responding to therapy (e.g., improvement, stabilization, or slowing of disease progression for pulmonary function or walking capacity).

   **Approval** is for **12 months**

II. **Brineura (cerliponase alfa)** is considered **medically necessary** for continuation of treatment of late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) when ALL the following criteria are met:
   a. Member has experienced a slowed loss of ambulation from baseline; and
   b. Member does not have acute intraventricular access device-related complications (e.g., leakage, device failure, or device-related infection) or ventriculoperitoneal shunts.

   **Approval** is for **12 months**

III. **Elaprase (idursulfase)** is considered **medically necessary** for continuation of treatment for mucopolysaccharidosis II (MPS II) who have a clinically positive response to therapy, which shall include improvement, stabilization, or slowing of disease progression.

**Approval** is for **12 months**

IV. **Fabrazyme (agalsidase beta)** is considered **medically necessary** for continuation of treatment of Fabry disease in members who are responding to therapy (e.g., reduction in plasma globotriaosylceramide [GL-3] or GL-3 inclusions, improvement and/or stabilization in renal function, pain reduction).

**Approval** is for **12 months**

V. **Kanuma (sebelipase alfa)** is considered **medically necessary** for continuation of treatment of lysosomal acid lipase (LAL) deficiency in members who are responding to therapy (e.g., improvement, stabilization, or slowing of disease progression for weight-for-age z-score if exhibiting growth failure, low-density lipoprotein [LDL], high-density lipoprotein [HDL], triglycerides, or alanine aminotransferase [ALT]).

**Approval** is for **12 months**

VI. **Lumizyme (alglucosidase alfa)** is considered **medically necessary** for continuation of treatment of Pompe disease in members 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).

**Approval** is for **12 months**

VII. **Nexviazyme (alglucosidase alfa-ngpt)** is considered **medically necessary** for continuation of treatment of late-onset Pompe disease in members who are responding to therapy (e.g., improvement, stabilization, or slowing of disease progression for motor function, walking capacity, respiratory function, or muscle strength).

**Approval** is for **12 months**

VIII. **Nulibry (fosdenopterin)** is considered **medically necessary** for continuation of treatment of MoCD Type A when one of the following is met:
   a. The member has received less than 12 months of therapy and has genetic testing results documenting a mutation in the molybdenum cofactor synthesis gene 1 *(MOSC1).*
   b. Member has received 12 months of therapy or more and is experiencing benefit from therapy (e.g., improvement, stabilization, or slowing of disease progression for encephalopathy, seizure activity, improved or normalized uric acid, urinary S-sulfocysteine, and xanthine levels).

**Approval** is for **12 months**

IX. **Mepsevii (vestronidase alfa-vjbk)** is considered **medically necessary** for continuation of treatment of mucopolysaccharidosis VII (MPS VII, Sly syndrome) in members who have a clinically positive response to therapy, which shall include improvement, stabilization, or slowing of disease progression.

**Approval** is for **12 months**

X. **Naglazyme (galsulfase)** is considered **medically necessary** for continuation of treatment of mucopolysaccharidosis VI (MPS VI, Maroteaux-Lamy syndrome) in members who have a clinically positive response to therapy, which shall include improvement, stabilization, or slowing of disease progression.

**Approval** is for **12 months**

XI. **Revcovi (elapegademase-lvlr)** is considered **medically necessary** for continuation of treatment of severe combined immunodeficiency disease (SCID) associated with adenosine deaminase (ADA) deficiency in members who are responding to therapy as evidenced by disease stability or disease improvement (e.g., normalization of plasma ADA activity, erythrocyte dATP levels, improvement of disease symptoms, etc.).

**Approval** is for **12 months**

XII. **Vimizim (elosulfase alfa)** is considered **medically necessary** for continuation of treatment of mucopolysaccharidosis type IVA (MPS IVA, Morquio A syndrome) in members who have a clinically positive response to therapy, which shall include improvement, stabilization, or slowing of disease progression.

**Approval** is for **12 months**

XIII. **Xenpozyme (olipudase alfa-rpcp)** is considered **medically necessary** for continuation of treatment of acid sphingomyelinase deficiency (ASMD) in adult and pediatric patients when ALL the following criteria are met:

a. The member meets Criteria for Initial Approval above and has achieved a positive clinical response to therapy as evidenced by an improvement, stabilization, or slowing of disease progression (e.g., improved or stabilized pulmonary function, splenomegaly, hepatomegaly, or platelet count)
b. Dose does not exceed 3 mg/kg every 2 weeks

**Approval** is for **12 months**

The enzyme replacement therapies in this policy are considered **not medically necessary** for members who do not meet the criteria set forth above.

Dosing and Administration

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

## CLINICAL RATIONALE

Background

Lysosomal storage diseases are inherited metabolic diseases that are characterized by an abnormal build-up of various toxic materials in the body's cells as a result of enzyme deficiencies. There are nearly 50 of these disorders altogether, and they may affect different parts of the body, including the skeleton, brain, skin, heart, and central nervous system. There is no cure for lysosomal storage disorders, and there are not yet specific treatments for many of these diseases. However, progress is being made in the search for therapies, and there are treatments available such as enzyme replacement therapy (ERT) which have been proven effective for some lysosomal storage disorders that greatly improve the quality of life for those affected.

Although the signs and symptoms vary from disease to disease in this group, symptoms occur in each case because of an enzyme deficiency that inhibits the ability of the lysosomes present in each of the body's cells to perform their normal function. The lysosomes function as the primary digestive units within cells. Their function is to break down complex components into simpler ones. Each cell has hundreds of lysosomes that degrade complex cellular components such as proteins (substrates) into simpler components. When this process does not take place, the substrate begins to accumulate in the cells. That is why these diseases are called "storage diseases". The symptoms of lysosomal storage disorders are generally progressive over a period of time.

**Fabry Disease**

On April 24, 2003, FDA approved Fabrazyme (Agalsidase beta), a recombinant human -galactosidase A (Gal A) enzyme for use in patients with Fabry disease. Fabry disease is a rare X-linked recessive lysosomal storage disorder that is caused by the deficient activity of -galactosidase A and the resultant accumulation of globotriaosylceramide and related glycosphingolipids. The major debilitating manifestations of Fabry disease result from the progressive accumulation of globotriaosylceramide in the vascular endothelium, leading to ischemia and infarction, especially in the kidney, heart and brain. The disease is panethnic with estimates of incidence range from 1 in 40,000 to 60,000 males. It predominantly affects males, although carrier (heterozygous) females also can be affected to a mild or severe degree because of random X-chromosomal inactivation.

Fabry patients can be divided into three categories of disease severity. In general, the severity of the disease is inversely correlated with enzyme activity.

- Hemizygotes (and some heterozygotes) with classical Fabry disease beginning in childhood, affecting many organ systems, and resulting in markedly decreased lifespan.
- Heterozygotes with mild to moderate disease or severe disease confined to a single organ system.
- Hemizygotes with residual enzyme activity who are diagnosed in the fourth, fifth, or sixth decade of life, when cardiac problems manifest (" cardiac variants").

Diagnosis of Fabry disease is confirmed by assay of galactosidase activity in leukocytes or plasma. In patients with the classic phenotype, levels of Gal A activity are very low or undetectable. Patients with detectable Gal A activity have a milder, variant phenotype. Female carriers can have normal to very low Gal A activity, therefore, their specific family mutation in the Gal A gene must be demonstrated. In addition, mutation or genetic linkage analysis may be necessary to establish carrier status. Most kindreds have family specific or private mutations; to date, more than 300 mutations have been identified.
The goal of enzyme replacement therapy is to prevent disease in young patients and both halt disease progression and reverse the underlying pathologic abnormalities and the resultant organ dysfunction in older patients. If plasma globotriaosylceramide levels prove to be a useful marker of disease burden and treatment efficacy, a goal of therapy may be to normalize plasma levels.

The safety and efficacy of Fabrazyme was established in a randomized, double-blind, placebo-controlled, multicenter clinical study in 82 adult patients with Fabry disease, all naïve to enzyme replacement therapy, evaluated time to first occurrence of a clinically significant event (renal, cardiac, or cerebrovascular event, or death). Patients received either Fabrazyme or placebo for up to 35 months (median follow up 18.5 months). A total of 14 of 51 (28%) of Fabrazyme-treated patients and 13 of 31 (42%) of placebo-treated patients experienced a clinically significant event. The estimated hazard ratio for the risk of clinically significant events was 0.57 (95% CI: 0.27, 1.22).

A long-term observational study assessed the rate of decline in renal function (eGFR) in 122 Fabrazyme treated patients (≥16 years) matched 1:1 with a cohort of 122 untreated patients matched based on age, sex, classic or non-classic Fabry disease subtype, and baseline estimated glomerular filtration rate (eGFR). The median follow-up time was 3 years in the untreated group and 4.5 years in the treated group, with a maximum of 5 years in both groups. The estimated mean slope of eGFR was -1.5 mL/min/1.73 $m^2$/year in

the Fabrazyme-treated group and -3.2 mL/min/1.73m$^2$/year in the untreated group with a treatment difference of 1.7 mL/min/1.73m$^2$/year (95% CI: 0.5, 3.0).

The most common adverse reactions which have occurred in ≥20% of patients treated with Fabrazyme and >2.5% compared to placebo are upper respiratory tract infection, chills, fever, headache, cough, burning or prickling sensation in the hands, arms, legs or feet, fatigue, accumulation of fluids causing swelling in lower limbs, dizziness, and rash.

In March 2021, FDA granted approval to Agalsidase beta (Fabrazyme) for the treatment of adult patients and pediatric patients 2 years of age and older with confirmed Fabry disease. The safety and efficacy of Fabrazyme in pediatric patients was established in an open-label, single-arm, multicenter study in 16 pediatric patients with Fabry disease aged 8 to 16 years (median 12 years). At baseline, patients had median plasma Î±GAL activity 0.2 nmol/hour/mL (range: 0.0, 2.0) and median leukocyte Î±GAL activity 0.5 nmol/hour/mg (range: 0.0, 12.5). All 14 males had elevated plasma GL-3 levels (i.e., >7.03 µg/mL) at baseline, whereas the two females had normal plasma GL-3 levels. Median eGFR was normal (112.1 mL/min/1.73 m$^2$) at baseline and did not change during treatment, and median urinary protein was 151.0 mg/24 hr (range: 70.0, 431.0). All patients received Fabrazyme 1 mg/kg every two weeks for up to 48 weeks. Safety and efficacy was established based on similar results in the adult population.
The most common adverse reactions in pediatric patients (>20%) were headache, abdominal pain, pharyngitis, fever, nausea, vomiting, rhinitis, diarrhea, arthralgia, and dizziness.

**Pompe Disease**
Pompe disease is an inherited disorder caused by the buildup of a complex sugar called glycogen in the body's cells. The accumulation of glycogen in certain organs and tissues, especially muscles, impairs their ability to function normally.

Researchers have described three types of Pompe disease, which differ in severity and the age at which they appear. These types are known as classic infantile-onset, non-classic infantile-onset, and late-onset.

1. The classic form of infantile-onset Pompe disease begins within a few months of birth. Infants with this disorder typically experience muscle weakness (myopathy), poor muscle tone (hypotonia), an enlarged liver (hepatomegaly), and heart defects. Affected infants may also fail to gain weight and grow at the expected rate (failure to thrive) and have breathing problems. If untreated, this form of Pompe disease leads to death from heart failure in the first year of life.
2. The non-classic form of infantile-onset Pompe disease usually appears by age one. It is characterized by delayed motor skills and progressive muscle weakness. The heart may be abnormally large (cardiomegaly), but affected individuals usually do not experience heart failure. The muscle weakness in this disorder leads to serious breathing problems, and most children with non-classic infantile-onset Pompe disease live only into early childhood.
3. The late-onset type of Pompe disease may not become apparent until later in childhood, adolescence, or adulthood. Late-onset Pompe disease is usually milder than the infantile-onset forms of this disorder and is less likely to involve the heart. Most individuals with late-onset Pompe disease experience progressive muscle weakness, especially in the legs and the trunk, including the muscles that control breathing. As the disorder progresses, breathing problems can lead to respiratory failure.

Lumizyme (alglucosidase alfa) provides an exogenous source of GAA, exerting enzymatic activity in cleaving glycogen. The U.S. Food and Drug Administration (FDA) has approved Lumizyme (alglucosidase alfa) for the treatment of patients with Pompe disease (GAA deficiency). Severe adverse reactions have occurred in patients receiving Lumizyme (alglucosidase alfa), including anaphylaxis, hypersensitivity reactions, immune-mediated reactions, and acute respiratory failure in patients with compromised cardiac and/or respiratory function. Due to these safety concerns, the FDA requires the prescribing information for Lumizyme (alglucosidase alfa) to include a black box warning.

Nexviazyme (avalglucosidase alfa-ngpt), an enzyme replacement therapy, to treat patients 1 year of age and older with late-onset Pompe disease. Nexviazyme is administered as an intravenous infusion. It is designed to improve the delivery of acid alpha-glucosidase (GAA), the enzyme lacking in patients with Pompe disease, to help reduce glycogen accumulation. The approval was supported by positive data from the Phase 3 COMET trial, which compared treatment with Nexviazyme to treatment with Lumizyme (alglucosidase alfa). In the study, patients treated with Nexviazyme demonstrated a 2.4-point greater improvement in forced vital capacity (FVC) percent-predicted compared with patients treated with Lumizyme at Week 49, supporting the noninferiority of Nexviazyme. In addition, in a measurement of functional endurance with a 6-minute walk test, patients treated with Nexviazyme walked 30 meters farther than patients treated with Lumizyme at Week 49, a key secondary endpoint. Nexviazyme was studied head-to-head versus Lumizyme in the Phase 3 clinical trial COMET, in which Nexviazyme was found to be noninferior to Lumizyme in measures of forced vital capacity and the 6-minute walk test. Nexviazyme did not meet the threshold for superiority, although numerical improvements were observed. The safety profile, improvements in lower-extremity muscle strength, and quality of life were also similar between the two therapies Administered as an intravenous (IV) infusion every other week, Nexviazyme is given at 20mg/kg for patients weighing 30kg (66 pounds) or less and 40mg/kg for those weighing more. Nexviazyme had previously received the FDA's Fast Track and Breakthrough Therapy designations for the treatment of patients with Pompe disease. The approval follows a priority review by the FDA.

**Mucopolysaccharidosis (MPS)**
Mucopolysaccharidoses (MPS) is a group of rare, inherited storage disorders are caused by the deficiency of specific lysosomal enzymes required for catabolism of glycosaminoglycans, which are long chains of carbohydrates. Glycosaminoglycans are used to help build bone, cartilage, tendons, corneas, skin, and connective tissues.

**Mucopolysaccharidosis Type I (MPS I)**
Mucopolysaccharidosis type I (MPS I) has a wide spectrum of clinical severity and has been subdivided into three phenotypes: Hurler Syndrome (severe), Hurler-Scheie syndrome (intermediate), and Scheie syndrome (mild). This disease is caused by a deficiency of a-L-iduronidase enzyme. Laronidase (Aldurazyme) is FDA approved for this condition.

**Hurler's syndrome** - most severe form, with neurologic, skeletal, and visceral involvement, including hepatosplenomegaly, cardiac disease, airway obstruction, mental retardation/development delay, corneal clouding, and severe skeletal abnormalities; death often occurs before the age of ten.
**Hurler-Scheie syndrome** - intermediate form characterized by slower progression of same types of complications, but with minimal-to-no mental retardation; death is usually later (e.g., 20s).
**Scheie's syndrome** - least severe with less extensive disease; some individuals may have a normal life span.

**Mucopolysaccharidosis Type II (MPS II)**
Mucopolysaccharidosis type II (MPS II), also known as Hunter syndrome, is an X-linked recessive disease caused by insufficient levels of lysosomal enzyme iduronate-2-sulfatase. There are 2 clinical subtypes of Hunter syndrome: MPS IIA and MPS IIB.
a condition that affects many different parts of the body and occurs almost exclusively in males. It is a progressively debilitating disorder; however, the rate of progression varies among affected individuals. Idursulfase (Elaprase) is FDA approved for this condition

At birth, individuals with MPS II do not display any features of the condition. Between ages two and four, they develop full lips, large, rounded cheeks, a broad nose, and an enlarged tongue (macroglossia). The vocal cords also enlarge, which results in a deep, hoarse voice. Narrowing of the airway causes frequent

upper respiratory infections and short pauses in breathing during sleep. As the disorder progresses, individuals need medical assistance to keep their airway open.

Many other organs and tissues are affected in MPS II. Individuals with this disorder often have a large head (macrocephaly), a buildup of fluid in the brain (hydrocephalus), an enlarged liver and spleen (hepatosplenomegaly), and a soft out-pouching around the bellybutton (umbilical hernia) or lower abdomen (inguinal hernia). People with MPS II usually have thick skin that is not very stretchy. Some affected individuals also have distinctive white skin growths that look like pebbles. Most people with this disorder develop hearing loss and have recurrent ear infections. Some individuals with MPS II develop problems with the light-sensitive tissue in the back of the eye (retina) and have reduced vision. Carpal tunnel syndrome commonly occurs in children with this disorder and is characterized by numbness, tingling, and weakness in the hand and fingers. Narrowing of the spinal canal (spinal stenosis) in the neck can compress and damage the spinal cord. The heart is also significantly affected by MPS II, and many individuals develop heart valve problems. Heart valve abnormalities can cause the heart to become enlarged (ventricular hypertrophy) and can eventually lead to heart failure.

**Mucopolysaccharidosis Type IVA (MPS IVA, B)**
Mucopolysaccharidoses type IV (MPS IVA, B), is also known as Morquio syndrome. It is a progressive disease with predominant skeletal manifestations, like skeletal abnormalities, loose joints, and underdevelopment of odontoid process. MPS IV has two subtypes: MPS IVA is due to N-acetylgalactosamine-6-sulfatase deficiency, and MPS IVB is due to beta- galactosidase deficiency. Of MPS IV subtypes, only MPS IVA can be treated with exogenous enzymes. The FDA approved elosulfase alfa (Vimizim™), for patients with MPS IVA or Morquio syndrome.

**Mucopolysaccharidosis Type VI (MPS VI)**
Mucopolysaccharidoses type VI (MPS VI), also known as Maroteaux-Lamy syndrome, is characterized by the absence or marked reduction in N-acetylgalactosamine 4-sulfatase. Galsulfase (Naglazyme®) is FDA approved for this condition.

**Mucopolysaccharidosis type VII (MPS VII)**
Mucopolysaccharidoses type VII (MPS VII), also known as Sly syndrome, is a deficiency in enzyme beta-glucuronidase. Vestronidase alfa-vjbk (Mepsevii™) is approved by the FDA for the treatment for this condition.

**Infantile Neuronal Ceroid Lipofuscinosis Type 2 (CLN2)**
On April 27, 2017, the FDA approved Brineura (cerliponase alfa), an enzyme replacement therapy, indicated 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 (TPP1) deficiency.

CLN2 disease is one of a group of disorders known as neuronal ceroid lipofuscinoses (NCLs), collectively referred to as Batten disease. 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. The initial symptoms usually 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 condition often require the use of a wheelchair by late childhood and typically do not survive past their teens. Batten disease is relatively rare, occurring in an estimated two to four of every 100,000 live births in the United States. Brineura is the first drug FDA approved to treat CLN2. Continuing studies will test its use for children under two years of age and its long-term effects over 10 years.

The FDA approval of Brineura was based on a non-randomized single-arm dose escalation clinical study with extension in symptomatic pediatric patients with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) disease, confirmed by TPP1 deficiency. Brineura-treated patients were compared to untreated patients from a natural history cohort. The Motor domain of a CLN2 Clinical Rating Scale was used to assess disease progression. Scores ranged from 3 (grossly normal) to 0 (profoundly impaired) with unit decrements representing milestone events in the loss of motor function (ability to walk or crawl). Twenty-four patients, aged 3 to 8 years were enrolled in the Brineura single-arm clinical study. One patient withdrew after week 1 due to inability to continue with study procedures; 23 patients were treated with Brineura 300 mg every other week for 48 weeks, and continued treatment during the extension period.
In the clinical study with extension, patients were assessed for decline in the Motor domain of the CLN2 Clinical Rating Scale at 48, 72 and 96 weeks. Decline was defined as having an unreversed (sustained) 2-category decline or an unreversed score of 0 in the Motor domain of the CLN2 Clinical Rating Scale. Patients' responses to Brineura treatment were evaluated if at screening a combined Motor plus Language CLN2 score of less than 6 was recorded. Two patients with a combined Motor plus Language CLN2 score of 6 were excluded from the analyses; they maintained that score throughout the study period. Motor scores of the 22 Brineura-treated patients in the clinical study with extension were compared to scores of the independent natural history cohort that included 42 untreated patients who satisfied inclusion criteria for the clinical study. The results of logistic modeling with covariates (screening age, screening motor score, genotype: 0 key mutations (yes/no)), demonstrated the odds of Brineura-treated patients not having a decline by 96 weeks were 13 times the odds of natural history cohort patients not having a decline [Odds Ratio (95% CI): 13.1 (1.2, 146.9)].

In an unadjusted non-randomized comparison, of the 22 patients treated with Brineura 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. Results from the natural history cohort demonstrated progressive decline in motor function; of the 42 patients in the natural history cohort 21 (50%) experienced an unreversed (sustained) 2-category decline or unreversed score of 0 in the Motor domain of the CLN2 Clinical Rating Scale over 96 weeks. To further assess efficacy, the 22 patients from the Brineura clinical study with a baseline combined Motor plus Language CLN2 score less than 6 were matched to 42 patients in the natural history cohort. Patients were matched based on the following covariates: baseline age at time of screening within 3 months, genotype (0, 1, or 2 key mutations), and baseline Motor domain CLN2 score at time of screening. Using the Motor domain of the CLN2 Clinical Rating Scale, decline was defined as having an unreversed 2-category decline or an unreversed score of 0. At 96 weeks, the matched analysis based on 17 pairs demonstrated fewer declines in the Motor domain for Brineura-treated patients compared to untreated patients in the natural history cohort.

**Lysosomal Acid Lipase Deficiency (LALD)**
Lysosomal acid lipase deficiency (LALD) is a rare, chronic, progressive, inherited disorder. If effects the body's ability to produce an enzyme called lysosomal acid lipase (LAL). This enzyme is needed for the breakdown fats (lipids) and cholesterol in the body. In affected individuals when the LAL enzyme is missing or deficient, fats (lipids) accumulate in organs and tissues throughout the body, primarily leading to liver disease (fibrosis, cirrhosis, and eventually liver failure). There are two forms of the condition. The most severe and rarest form begins in infancy. The less severe form can begin from childhood to late adulthood.

In December 2015, the U.S. Food and Drug Administration (FDA) approved Kanuma (sebelipase alfa), the first therapy that treats the underlying cause of the disease. Previously, there were only supportive therapies available for LALD.

**Molybdenum Cofactor Deficiency Type A**
Molybdenum cofactor deficiency (MoCD) is a rare inherited metabolic disorder characterized by neonatal onset intractable seizures, dysmorphic facies, dislocated ocular lenses, and severe psychomotor retardation. Infants with this condition appear normal at birth, but within a week have difficulty feeding and

develop seizures that do not improve with treatment. Brain abnormalities, including atrophy of brain tissue, lead to severe developmental delay and affected individuals usually exhibit loss of individual function. Molybdenum cofactor deficiency is a rare condition that is estimated to occur in 1 in 100,000 to 200,000 newborns worldwide. The disease is caused by mutations in the MOCS1, MOCS2, or GPHN gene, and there are three forms of the disorder, named types A, B, and C (or complementation groups A, B, and C). MOCS1 gene mutations cause type A, MOCS2 gene mutations cause type B, and GPHN gene mutations cause type C, although the signs and symptoms of each form overlap. The proteins produced from each of these genes are involved in the biosynthesis of molybdenum cofactor, which is essential to the function of several enzymes. These enzymes help break down (metabolize) different substances in the body, some of which are toxic if not metabolized. Mutations in the MOCS1, MOCS2, or GPHN gene reduce or eliminate the function of the associated protein, which impairs molybdenum cofactor biosynthesis and metabolic enzyme function. The resulting loss of enzyme activity leads to buildup of sulfite, S-sulfocysteine, xanthine, hypoxanthine, and low levels of uric acid in the blood. Sulfite build-up is toxic to the brain, and researchers suggest that damage caused by the abnormally high levels of sulfite leads to encephalopathy, seizures, and the other features of molybdenum cofactor deficiency. Nulibry is a cyclic pyranopterin monophosphate (cPMP) agent FDA approved to reduce the risk of mortality in patients with molybdenum cofactor deficiency (MoCD) Type A, although affected individuals usually do not survive past early childhood.

On February 28, 2021, the FDA approved Nulibry (fosdenopterin) a cyclic pyranopterin monophosphate (cPMP) indicated to reduce the risk of mortality in patients with molybdenum cofactor deficiency (MoCD) Type A.

The safety and efficacy of Nulibry was based on results from 2 prospective open-label single-arm dose escalation studies and 1 retrospective observational study in patients with a confirmed diagnosis of MoCD Type A. Efficacy of Nulibry and rcPMP were assessed in a combined analysis of 13 patients with genetically confirmed MoCD Type A from Study 1 (n=8), Study 2 (n=1), and Study 3 (n=4) who received substrate replacement therapy with Nulibry or rcPMP. Patients treated with Nulibry were titrated from their initial dose to a maximum of 0.9 mg/kg administered once daily as an intravenous infusion. Efficacy was assessed by comparing overall survival in pediatric patients treated with Nulibry or rcPMP (n=13) with an untreated natural history cohort of pediatric patients with genetically confirmed MoCD Type A who were genotype-matched to the treated patients (n=18). Patients treated with Nulibry or rcPMP had an improvement in overall survival compared to the untreated, genotype-matched, historical control group. Kaplan Meier estimates for overall survival in patients treated with Nulibry or rcPMP vs. control group showed that 92% of treated patients had a 1-year survival probability vs. 67% in the control group, and 84% of treated patients had a 3-year survival probability vs. 55% in the control group. For patients treated with Nulibry or rcPMP, there were 2 deaths (15%) total vs. 12 deaths (67%) seen in the control group. Treatment with Nulibry resulted in a reduction in urine concentrations of SSC in patients with MoCD Type A and the reduction was sustained with long-term treatment over 48 months. Following treatment with Nulibry in Studies 1 and 2 (n=9), the mean ± SD levels of urinary SSC normalized to creatinine ranged from 11 (±8.5) to 7 (±2.4) Î¼mol/mmol from Month 3 to Month 48.

The most common adverse reactions (>25%) were catheter-related complications, pyrexia, viral infection, pneumonia, otitis media, vomiting, cough/sneezing, viral upper respiratory infection, gastroenteritis, bacteremia, and diarrhea. Caregivers should be advised to avoid patient exposure to sunlight due to photosensitivity risk

**Acid Sphingomyelinase Deficiency (ASMD)**

Acid sphingomyelinase deficiency (ASMD), also known as Niemann-Pick disease, is a rare progressive genetic disorder in which there is a mutation of sphingomyelin phosphodiesterase 1 (SMPD1) gene resulting in a deficiency in the enzyme acid sphingomyelinase (ASM). ASM metabolizes sphingomyelin, and a deficiency of ASM will result in accumulation of sphingomyelin in various tissues causing hepatomegaly, splenomegaly, respiratory complications when accumulating in the lungs, and potentially

other symptoms depending on the individual patient. Initial diagnosis and classification can be difficult and is made based on factors including age of onset and the severity of symptoms. Type A ASMD is an aggressive form generally seen in infants causing neurologic deterioration, severe hepatosplenomegaly, jaundice, ascites, and other gastrointestinal or respiratory symptoms leading to failure to thrive and is often fatal by 3 years of age. Types A/B and B ASMD may be seen in a range of ages from infancy to adulthood, lead to more mild symptoms, and rarely involve neurological disorders. Types A/B and B have variety of symptoms based on the tissue sphingomyelin is accumulating in and may include: hepatosplenomegaly causing low platelet levels, scarring of the liver, or dyslipidemia; gradual deterioration of lung function causing dyspnea or recurrent respiratory infections; children may experience delays in growth and development; osteopenia and bone pain; in rare cases of central nervous system involvement, nystagmus, ataxia, peripheral neuropathy, abnormalities of the retina, and psychiatric disorders have been reported. It is estimated that 1 in 250,000 individuals in the US have ASMD, but that number may be underestimated due to the difficulty in properly diagnosis this disorder.

On August 31, 2022 the FDA approved Xenpozyme (olipudase alfa-rpcp) as the first medication indicated for adult and pediatric patients with acid sphingomyelinase deficiency (ASMD). Xenpozyme (olipudase alfa-rpcp) for intravenous infusion is an exogenous source of ASM for the treatment of non-central nervous system manifestations of ASMD.

Xenpozyme (olipudase alfa-rpcp) showed superiority to placebo in a phase II/III international, double-blind, placebo-controlled trial of adults (ASCEND; N=36) in improving lung function (22% vs 3%), decreasing liver (-28% vs -1.5%%) and spleen (-39% vs 0.5%) volumes, and increasing platelet count (17% vs 2.5%) compared to baselines at week 52 of the trial. For pediatric patients, Xenpozyme (olipudase alfa-rpcp) demonstrated efficacy in a phase I/II, multicenter, open-label, single arm trial of pediatric patients (ASCEND-Peds; N=20) by improving lung function (diffusing capacity of the lung for carbon monoxide increase by 33%; p=0.0053), improving least square mean percent change from baseline for splenomegaly and hepatomegaly (>40%; p<0.0001), increased platelet count (34%: p=0.0003), and height Z-scores (0.56; p<0.0001) at week 52.

Xenpozyme (olipudase alfa-rpcp) carries a black box warning regarding severe hypersensitivity reactions including anaphylaxis that requires immediate availability of medical support measures, including cardiopulmonary resuscitation equipment, during Xenpozyme administration. Additionally, if a patient experiences a severe hypersensitivity reaction, a desensitization procedure to Xenpozyme should be considered. Elevated transaminases have been noted and baseline alanine aminotransferase (ALT)/aspartate aminotransferase (AST) is recommended one month prior to initiation and periodically during therapy. Other common adverse events included headache, cough, diarrhea, hypotension, ocular hyperemia, pyrexia, rhinitis, and abdominal pain.

## PROCEDURES AND BILLING CODES

***To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.***

- J1931 - Injection, laronidase, (Aldurazyme), 0.1 mg
- J0567 - Injection, cerliponase alfa, (Brineura), 1 mg
- J1743 - Injection, idursulfase, (Elaprase), 1 mg
- J0180 - Injection, agalsidase beta, (Fabrazyme), 1 mg
- J2840 - Injection, sebelipase alfa, (Kanuma), 1 mg
- J0221 - Injection, alglucosidase alfa, (Lumizyme), 10 mg
- J3397 - Injection, vestronidase alfa-vjbk, (Mepsevii), 1 mg
- J1458 - Injection, galsulfase, (Naglazyme),1 mg
- J1322 - Injection, elosulfase alfa, (Vimizim), 1 mg

- J0220 - Injection, alglucosidase alfa, 10 mg, not otherwise specified
- C9399 - Unclassified drugs or biologicals
- C9085 - Injection, avalglucosidase alfa-ngpt, (Nexviazyme), 4 mg – cancelled 4/1/2022
- J0219 – Injection, avalglucosidase alfa-ngpt, (Nexviazyme), 4 mg – effective 4/1/2022
- J3490 - Unclassified drugs
- J3590 - Unclassified biologics

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## POLICY HISTORY

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