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Policy Number: 010.004

Title: Coverage Determination Policy for Enzyme Replacement Therapy (ERT)

- **Fabrazyme (Agalsidase Beta); Lumizyme (Alglucosidase Alfa); VPRIV (Velaglucerase Alfa); Cerezyme (Imiglucerase); Kanuma (Sebelipase alfa); Xenpozyme (Olipudase alfa-rpcp); Nexviazyme (Avalglucosidase alfa-ngpt)**

Regions: ☒ **Texas** ☐ **Florida** ☐ **Indiana** ☐ **New Jersey** ☒ **New Mexico**

Impacted Areas:

☒ Network Management/Provider Services	☒ Utilization Management
☐ Member services	☐ Case management
☐ Quality Management	☐ Disease management
☐ Credentialing	☒ Claims
☐ IT	☐ Human resources
☐ Administration	☐ Finance
☐ Compliance/delegation	☒ Pharmacy
	☐ ALL

Available LCD/NCD/LCA: None

Disclaimer:

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Coverage Policy Number: 010.004

Line of Business: Medicare Part B

Policy Type: Prior Authorization

Coverage Determination

(Initial/New Requests)

Agalsidase beta (Fabrazyme) is medically necessary for the treatment of **Fabry disease** when **ALL** the following criteria are met:

A. Diagnosis of Fabry disease as confirmed by **ONE** of the following:

   I. Absence or deficiency (< 5% of mean) of normal alpha-galactosidase A (α-Gal A) enzyme activity in leukocytes, dried blood spots, or serum analysis

   II. Molecular genetic testing for deletion or mutations in the galactosidase alpha gene

B. Presence of clinical signs and symptoms of the disease (e.g., Acroparesthesias, angiokeratomas, whorls, anhidrosis/hypohidrosis, renal disease, exercise/heat/cold intolerance,etc.)

C. Dosing is in accordance with the United States Food and Drug Administration approved labeling

Alglucosidase alfa (Lumizyme) is medically necessary for the treatment of **Pompe disease** when **ONE** of the following criteria are met:

A. **ALL** of the following for infantile-onset Pompe disease:

   I. Diagnosis of infantile-onset Pompe disease as confirmed by **ONE** of the following:

      a. Absence or deficiency (<1% of the lab specific normal mean) of acid alpha-glucosidase (GAA) activity in skin fibroblasts

      b. Molecular genetic testing for deletion or mutations in the GAA gene

   II. Presence of clinical signs and symptoms of the disease (e.g., cardiac hypertrophy, respiratory distress, skeletal muscle weakness, etc.)

   III. Dosing is in accordance with the United States Food and Drug Administration approved labeling

B. **ALL** of the following for late-onset (non-infantile) Pompe disease:

   I. Diagnosis of late-onset Pompe disease as confirmed by **ONE** of the following:

      a. Absence or deficiency (<40% of the lab specific normal mean) of acid alpha-glucosidase (GAA) activity in lymphocytes, fibroblasts or muscle

      b. Molecular genetic testing for deletion or mutations in the GAA gene

   II. Presence of clinical signs and symptoms of the disease (e.g., cardiac hypertrophy, respiratory distress, skeletal muscle weakness, etc.)

   III. Dosing is in accordance with the United States Food and Drug Administration approved labeling

Imiglucerase (Cerezyme) is medically necessary for the treatment of **Type 1 Gaucher disease** when **ALL** of the following criteria are met:

A. Diagnosis of Type 1 Gaucher disease

B. **ONE** of the following:

   I. History of failure of VPRIV due to failure to meet clinical goals (e.g., persistent anemia, thrombocytopenia, bone disease, hepatomegaly, or splenomegaly) despite VPRIV therapy

   II. History of failure of VPRIV due to hypersensitivity to VPRIV therapy

C. Dosing is in accordance with United States Food and Drug Administration (FDA) approved labeling

Velaglucerase Alfa (VPRIV) is medically necessary for the treatment of **Type 1 Gaucher disease** when **ALL** of the following criteria are met:

A. Diagnosis of Type 1 Gaucher disease

B. Symptomatic disease (e.g., moderate to severe anemia, thrombocytopenia, bone disease, hepatomegaly, splenomegaly)

C. Dosing is in accordance with United States Food and Drug Administration (FDA) approved labeling

Imiglucerase (Cerezyme) are proven and medically necessary for the treatment of **Type 3 Gaucher disease** when **ALL** of the following criteria are met:

A. Diagnosis of Type 3 Gaucher disease

B. Symptomatic disease (e.g., moderate to severe anemia, thrombocytopenia, bone disease, hepatomegaly, splenomegaly)

C. **ONE** of the following:

   I. History of failure of VPRIV due to failure to meet clinical goals (e.g., persistent anemia, thrombocytopenia, bone disease, hepatomegaly, or splenomegaly) despite VPRIV therapy

   II. History of failure of VPRIV due to hypersensitivity to VPRIV therapy

D. Dosing does not exceed 60units/kg every 2 weeks

Velaglucerase Alfa (VPRIV) is medically necessary for the treatment of **Type 3 Gaucher disease** when **ALL** of the following criteria are met:

A. Diagnosis of Type 3 Gaucher disease

B. Symptomatic disease (e.g., moderate to severe anemia, thrombocytopenia, bone disease, hepatomegaly, splenomegaly)

C. Dose does not exceed 60 units/kg every 2 weeks

Sebelipase alfa (Kanuma) is proven and medically necessary for the treatment of **Lysosomal Acid Lipase Deficiency [LAL-D, Wolman disease (WD), Cholesteryl Ester Disease (CESD)]** when **ALL** of the following are met:

A. Diagnosis of lysosomal acid lipase deficiency [LAL-D, Wolman disease (WD), cholesteryl ester disease (CESD)] as confirmed by **ONE** of the following:
    I. Absence or deficiency lysosomal acid lipase activity by dried blood spot test
    II. Molecular genetic testing for deletion or mutations in the lipase A, lysosomal acid type (LIPA) gene
B. Presence of clinical signs and symptoms of the disease (e.g., abdominal distention, hepatosplenomegaly, liver fibrosis, ascites, etc.)
C. Dosing is in accordance with the United States Food and Drug Administration approved labeling

Olipudase alfa-rpcp (Xenpozyme) is proven and medically necessary for the treatment of **Acid Sphingomyelinase Deficiency (ASMD)** when **ALL** of the following are met:

A. Diagnosis of acid sphingomyelinase deficiency (ASMD) type A/B or B confirmed by **ONE** of the following:
    I. Absence or deficiency of acid sphingomyelinase (ASM) enzyme activity
    II. Molecular genetic testing for mutations in the SMPD1 gene
B. Presence of clinical signs and symptoms of the disease (e.g., hepatosplenomegaly, elevated transaminases, mixed dyslipidemia, abnormal pulmonary function)
C. Xenpozyme is not being used to treat central nervous system (CNS) manifestations of ASMD
D. Dosing is in accordance with the United States Food and Drug Administration approved labeling

Avalglucosidase alfa-ngpt (Nexviazyme) is proven and medically necessary for the treatment of late-onset Pompe disease when ALL the following criteria are met:

A. Diagnosis of late-onset Pompe disease as confirmed by one the following:
    I. Absence or deficiency (< 40% of the lab specific normal mean) acid alpha-glucosidase deficiency (GAA) activity in lymphocytes, fibroblasts or muscle
    II. Molecular genetic testing for deletion or mutations in the GAA gene
B. Presence of clinical signs and symptoms of the disease (e.g., cardiac hypertrophy, respiratory distress, skeletal muscle weakness, etc.); and
C. Dosing is in accordance with the United States Food and Drug Administration approved labeling

(Renewal/Continuation of Therapy Requests)

RENEWAL criteria for **Fabrazyme:**

1. Patient has previously received treatment with Fabrazyme
2. Patient has experienced a positive clinical response to therapy (e.g., improved renal function, reduction in mean plasma GL-3 levels, decreased GL-3 inclusions, etc.)
3. Dosing is in accordance with the United States Food and Drug Administration approved labeling

RENEWAL criteria for **Lumizyme:**

1. Patient has previously received treatment with Lumizyme
2. Patient has experienced a positive clinical response to therapy (e.g., improved respiratory/cardiac function, improved endurance, etc.)
3. Dosing is in accordance with the United States Food and Drug Administration approved labeling

RENEWAL criteria for **Velaglucerase Alfa (VPRIV)** and **Imiglucerase (Cerezyme) for Type 1 Gaucher disease:**

1. Patient has previously received treatment with VPRIV or Cerezyme
2. Patient has experienced a positive clinical response to therapy (reduced severity or resolution of anemia, thrombocytopenia, bone disease, hepatomegaly, splenomegaly)
3. Dosing is in accordance with the United States Food and Drug Administration approved labeling

RENEWAL criteria for **Velaglucerase Alfa (VPRIV)** and **Imiglucerase (Cerezyme) for Type 3 Gaucher disease:**

1. Patient has previously received treatment with VPRIV or Cerezyme
2. Patient has experienced a positive clinical response to therapy (reduced severity or resolution of anemia, thrombocytopenia, bone disease, hepatomegaly, splenomegaly)
3. Dose does not exceed 60units/kg every 2 weeks

RENEWAL criteria for **Kanuma:**

1. Patient has previously received treatment with Kanuma
2. Patient has experienced a positive clinical response to Kanuma therapy [e.g., improved disease symptoms, improvement of laboratory values (LFTs, cholesterol, triglycerides), etc.]
3. Dosing is in accordance with the United States Food and Drug Administration approved labeling

RENEWAL criteria for **Xenpozyme:**

1. Patient has previously received treatment with Xenpozyme
2. Patient has experienced a positive clinical response to Xenpozyme therapy (e.g., reduced spleen volume, reduced liver volume, improved liver transaminase levels, improved lipid profile, improved pulmonary function)
3. Dosing is in accordance with the United States Food and Drug Administration approved labeling

RENEWAL criteria for **Avalglucosidase alfa-ngpt (Nexviazyme)**:

1. Patient has previously received treatment with avalglucosidase alfa-ngpt therapy
2. Patient has experienced a positive clinical response to avalglucosidase alfa-ngpt therapy (e.g., improved respiratory/cardiac function, improved endurance, etc.)
3. Dosing is in accordance with the United States Food and Drug Administration approved labeling

FDA Approved Dose and Indication

FDA approved indications	Approved Dosing
Fabrazyme is indicated for the treatment of **Fabry disease**	• 1 mg/kg IV infusion every 2 weeks
Lumizyme is indicated for patients with **Pompe disease**	• 20 mg/kg IV infusion every 2 weeks
VPRIV is indicated for long-term enzyme replacement therapy (ERT) for patients with **Type 1 Gaucher disease**	• **Patients Naive to Enzyme Replacement Therapy:** 60 Units/kg every other week • **Patients switching from imiglucerase:** Initiate at previous imiglucerase dose 2 weeks following the last imiglucerase dose, max dose of 60 units/kg every other week
Cerezyme is indicated for long-term enzyme replacement therapy (ERT) for patients with **Type 1 Gaucher disease**	• Initial, 2.5 units/kg 3 times weekly to max dose of 60 units/kg once every 2 weeks
Kanuma is indicated for **Lysosomal Acid Lipase Deficiency**	• 1 mg/kg as an intravenous infusion once every other week • For suboptimal clinical response (ie, poor growth, deteriorating biochemical markers, and/or parameters of lipid metabolism), increase to 3 mg/kg once every other week
Xenpozyme is indicated for **Acid Sphingomyelinase Deficiency (ASMD)**	• **Initial:** 0.1 mg/kg via IV infusion (Day 1/Week 0) Weight based dosing information, patients with body mass index (BMI) less than or equal to 30, the dosage is based on actual body weight (kg); greater than 30, the dosage is based on adjusted body weight (kg) • **Dose escalation regimen:** Day 1/Week 0, 0.1 mg/kg; second dose (Week 2), 0.3 mg/kg; third dose (Week 4), 0.3 mg/kg; fourth dose (Week 6), 0.6 mg/kg; fifth dose (Week 8), 0.6 mg/kg; sixth dose (Week 10), 1 mg/kg; seventh dose (Week 12), 2 mg/kg; eighth dose (Week 14), 3 mg/kg • **Maintenance:** 3 mg/kg IV infusion every 2 weeks
Nexviazyme is indicated for late-onset Pompe disease	• **≥ 30 kg:** 20 mg/kg (Actual Body Weight) every 2 weeks • **<30 kg:** 40 mg/kg (Actual Body Weight) every 2 weeks

General Background

Agalsidase Beta (Fabrazyme) is approved for use in patients with Fabry disease to decrease globotriaosylceramide (GL-3) deposition in capillary endothelium of the kidney and other cell types

Fabry disease is an X-linked genetic disorder of glycosphingolipid metabolism. Deficiency of the lysosomal enzyme alpha-galactosidase A leads to progressive accumulation of glycosphingolipids, predominantly globotriaosylceramide (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 play a role in renal failure. Agalsidase beta provides an exogenous source of alpha-galactosidase A in Fabry disease patients. Nonclinical and clinical studies evaluating a limited number of cell types indicate that agalsidase beta will catalyze the hydrolysis of glycosphingolipids, including GL-3.

Alglucosidase Alfa (Lumizyme) is indicated for patients with Pompe disease (acid alpha-glucosidase (GAA) deficiency). Alglucosidase alfa is a recombinant human enzyme, acid alpha-glucosidase (GAA), produced in a Chinese hamster ovary cell line. Alglucosidase alfa provides an exogenous source of GAA, the enzyme that is absent or deficient in Pompe disease (glycogen storage disease type II). Alglucosidase alfa binds to mannose-6-phosphate receptors on the cell surface of lysosomes and is internalized and transported into lysosomes. Proteolytic cleavage occurs, resulting in increased enzymatic activity in cleaving glycogen. Alglucosidase alfa cleaves glycogen by catalyzing the hydrolysis of alpha-1,4- and alpha-1,6-glycosidic linkages of lysosomal glycogen.

Velaglucerase Alfa (VPRIV) is indicated for long-term enzyme replacement therapy (ERT) in adults and pediatric patients 4 years and older with type 1 Gaucher disease. Clinical studies have demonstrated the efficacy of velaglucerase alfa in non-neuropathic Gaucher disease as initial treatment among patients with no prior ERT exposure and among patients switching from imiglucerase to velaglucerase alfa. Velaglucerase alfa is an enzyme created by gene activation technology in human fibroblast cells. Velaglucerase alfa catalyzes hydrolysis of glucocerebroside normally accomplished by the enzyme beta-glucocerebrosidase. In patients deficient in lysosomal enzyme beta-glucocerebrosidase (Gaucher disease), velaglucerase alfa will catalyze conversion of sphingolipid glucocerebroside into glucose and ceramide, thereby reducing the accumulation of glucocerebroside in the lysosomal compartment of macrophages (Gaucher cells) and subsequent accumulation of Gaucher cells in the liver, spleen, bone marrow and other organs. Accumulation of Gaucher cells in the liver and spleen causes organomegaly.

Cerezyme (Imiglucerase) is indicated for long-term enzyme replacement therapy (ERT) in pediatric and adult patients with type 1 Gaucher disease. Glucocerebrosidase is an enzyme found to be deficient in Gaucher's disease. Imiglucerase is an analogue of the human enzyme beta-glucocerebrosidase produced by recombinant DNA technology. Imiglucerase catalyzes the hydrolysis of glucocerebroside to glucose and ceramide. In clinical trials, imiglucerase improved anemia and thrombocytopenia, reduced spleen and liver size, and decreased cachexia.

Medicare does not have a National Coverage Determination (NCD) for the Enzyme Replacement Therapies listed in this policy. Local Coverage Determinations (LCDs) for Texas, for the Enzyme Replacement Therapies listed in this policy, do not exist at this time.

Sebelipase alfa (Kanuma) is indicated for long-term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase (LAL) deficiency. It is a recombinant human lysosomal acid lipase (rhLAL). Lysosomal acid lipase is a lysosomal glycoprotein enzyme that catalyzes the hydrolysis of cholesteryl esters to free cholesterol and fatty acids and the hydrolysis of triglycerides to glycerol and free fatty acids. Sebelipase alfa binds to cell surface receptors via glycans expressed on the protein and is subsequently internalized into lysosomes. Sebelipase alfa catalyzes the lysosomal hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol and free fatty acids.

Olipudase alfa-rpcp (Xenpozyme) is a recombinant hydrolytic lysosomal human acid sphingomyelinase (ASM) enzyme designed to reduce sphingomyelin (SM) accumulation in the liver, spleen, and lung of patients with acid sphingomyelinase deficiency (ASMD). It provides exogenous ASM, replacing deficient or defective ASM caused by pathogenic variants in the sphingomyelin phosphodiesterase 1 gene (SMPD1). Olipudase alfa-rpcp is not expected to cross the blood-brain barrier or modulate the CNS manifestations of ASMD

Avalglucosidase alfa-ngpt (**Nexviazyme**) is a recombinant hydrolytic lysosomal glycogen-specific human α-glucosidase enzyme that is conjugated with multiple synthetic bis-mannose-6-phosphate (M6P) and is produced in Chinese hamster ovary cells. M6P on avalglucosidase alfa-ngpt mediates the binding to M6P receptors on the cell surface, that is then internalized and transported into lysosomes. It then undergoes proteolytic cleavage resulting in increased GAA enzymatic activity. This allows for avalglucosidase alfa-ngpt to exert enzymatic activity, thereby cleaving glycogen.

Precautions and Warnings

Fabrazyme

- Life-threatening anaphylactic reaction, severe allergic reactions, Infusion-related reactions and development of IgE antibodies or skin test reactivity may occur during Fabrazyme infusions.

Lumizyme- Black Box Warning

- Life-threatening anaphylactic reactions, severe hypersensitivity reactions and Immune-mediated reactions have occurred in some patients during and after alglucosidase alfa infusions.
- Infantile-onset Pompe disease patients with compromised cardiac or respiratory function may be at risk of serious acute cardiorespiratory failure due to fluid overload, and require additional monitoring.

VPRIV

- Hypersensitivity reactions, including anaphylaxis, may occur during the first 6 months of treatment.

Cerezyme

- Development of IgG antibody and Anaphylactoid reactions are possible adverse effects with cerezyme treatment.

Clinical Evidence

Agalsidase Beta (Fabrazyme) in a randomized, double-blind, placebo-controlled study of Fabry disease patients with kidney dysfunction (n=82), agalsidase beta appeared to delay the time to renal, cardiovascular, and cerebrovascular events. Patients with Fabry disease (aged 16 years and older) and kidney dysfunction (serum creatinine 1.2 to less than 3 milligrams/deciliter (mg/dL) or creatinine clearance less than 80 milliliters/minute) were randomized (2:1) to intravenous infusions of either 1 mg/kilogram (kg) agalsidase beta (n=51) or placebo (n=31) every two weeks. All patients were pretreated with acetaminophen or ibuprofen with or without an antihistamine prior to infusion. Primary endpoint clinical events included a 33% increase in serum creatinine, progression to end-stage kidney disease, arrhythmia, angina, myocardial infarction, stroke, transient ischemic attack, or death. Clinical events occurred in 27% of the agalsidase beta group and 42% of the control group; although suggestive of treatment efficacy, statistical significance with intent-to-treat analysis was not achieved (p=0.06). Proteinuria was strongly associated with any clinical event (hazard ratio (HR) 1.3, 95% confidence interval (CI) 1.1 to 1.6; p=0.005) and renal specific events (HR 1.4, 95% CI 1.2 to 1.8; $p < 0.001$) therefore secondary analysis were conducted to adjust for baseline proteinuria. Sub-analysis of renal events in protocol-adherent patients (n=74) revealed a significant treatment effect in the agalsidase beta group versus placebo after adjustment for proteinuria (HR 0.39, 95% CI 0.16 to 0.93; p=0.034) which implies earlier intervention may be more efficacious than intervention during advanced disease. Analysis of the other clinical events suggested agalsidase beta efficacy but study limitations, including small sample size and low event rate within the limited time frame, prevented achievement of statistical significance. Safety data showed the most common treatment related adverse effects were mild to moderate infusion reactions, occurring in 55% of agalsidase beta patients and 23% of placebo patients. Three patients experienced serious treatment related effects including severe hypotension, urticaria, throat congestion, rigors and fever. Three patients died during the study, 2 in the agalsidase group (multiple pulmonary emboli and cardiac arrest) and 1 in the placebo group (cardiac arrest following a stroke).

b) Open controlled studies have indicated benefits of intravenous agalsidase beta in patients with classic Fabry's disease. Significant reductions in globotriaosylceramide (Gb3) concentrations were observed in plasma and tissues, including liver, heart, kidney, and skin, which tended to be dose-dependent. The optimal dose appears to be 1 milligram/kilogram (mg/kg) every other week. This schedule was more effective in producing Gb3 tissue clearance than dosing every 2 days in a phase II study. Agalsidase beta was reported to reduce pain and improve quality of life in a small open study but not in a placebo- controlled trial.

c) In a double-blind, placebo-controlled study involving 58 patients with classic Fabry's disease, biweekly infusions of 1 mg/kg were highly effective in clearing renal microvascular endothelial deposits of Gb3 (primary study endpoint); following 20 weeks of treatment, clearance was achieved in 69% and 0% of patients receiving agalsidase beta and placebo, respectively (p less than 0.001). Significant reductions in plasma Gb3 and microvascular deposits of Gb3 in skin and endomyocardium were also demonstrated via biopsy; median plasma Gb3 levels declined from a mean of 14.5 nanograms (ng)/microliter at baseline to less than 1.2 ng/microliter after 14 weeks of treatment, and plasma Gb3 levels correlated with tissue clearance. With continued

treatment in an open-label extension of this trial (6 months), clearance of microvascular deposits of Gb3 was maintained or further reduced; clearance of renal microvascular endothelial Gb3 deposits after 6 months was evident in 98% of biopsied patients who had previously received agalsidase beta and in 100% of patients who had switched from placebo. The clearance of endomyocardial microvascular endothelial deposits was increased by an additional 15% after a further 6 months of therapy. Pain severity related to Fabry's disease and associated quality of life were, however, not improved to a significant degree by agalsidase beta. Other medications, including analgesics, were taken concurrently by patients in this study; types of analgesics and numbers of patients taking them were not specified in baseline data, and this (or a strong placebo effect) may have accounted for lack of an effect of treatment on pain/quality of life

Alglucosidase Alfa (Lumizyme) In an open-label study, infants treated with IV alglucosidase alfa (n=21) for a median of 120 weeks had a 79% reduced risk of death compared with untreated historical controls (n=86), and a 58% reduction in the risk of requiring invasive ventilation. A 3-year study revealed that ventilation-free survival to 24 months of age was 66.7%, and to 36 months of age was 49.4%. Only 1 of 61 patients in the untreated historical control group survived to 24 and 36 months of age.

In a randomized trial (N=90) of treatment-naive patients aged 10 to 70 years with late-onset Pompe disease, 78 weeks of alglucosidase alpha therapy significantly increased the distance walked on a 6-minute test by a mean of 28 meters and increased percent of predicted forced vital capacity (FVC) by a mean of 1.3% compared with placebo. These improvements were generally maintained during a 26-week open-label extension (N=55). After 104 weeks of treatment, the 6-minute walking test increased by a mean of 21.3 meters from baseline and percent of predicted FVC increased by a mean of 0.8% from baseline.

Velaglucerase Alfa (VPRIV)
Treatment-naive
In patients aged 4 years and older, efficacy was established during 2 randomized trials (N=59) with study duration of 9 to 12 months. Velaglucerase improved platelet count, decreased liver and spleen volume, and significantly improved Hb concentration (2.4 g/dL mean change from baseline) at 12 months.
Switching from imiglucerase
In patients aged 9 years and older, velaglucerase alfa provided stable Hb and platelet counts when switched from imiglucerase therapy in a small, single-arm study (N=40).

Imiglucerase (Cerezyme) In a randomized, double blind, non-inferiority trial comparing velaglucerase alfa and imiglucerase in treatment naïve children and adults with GD1, velaglucerase alfa was observed to be non-inferior to imiglucerase. Differences in immunogenicity were also observed.
For the past 15 years, the standard of care for symptomatic GD1 has been enzyme replacement therapy with imiglucerase. This recombinant, infusible enzyme is produced in Chinese hamster ovary cells and differs from the wild-type human enzyme sequence by a single amino-acid substitution at position 495 that does not appear to affect catalytic activity. Imiglucerase has been proven to be safe and effective in clinical trials, and efficacy has also been shown in multiple

studies from the International Collaborative Gaucher Group (ICGG) Registry. The long-term safety of imiglucerase was shown in an international monitoring database.

Sebelipase alfa (Kanuma)

Burton et al conducted a phase 3 clinical trial to evaluate the safety and efficacy of enzyme-replacement therapy with sebelipase alfa.19 This study was a multicenter, randomized, double-blind, placebo-controlled trial, enrolling 66 patients. Patients were randomized 1:1 to receive placebo (N = 30) or sebelipase alfa (N = 36) administered intravenously at 1mg/kg every other week. The placebo-controlled phase of the study was 20 weeks long, followed by an open-label treatment for all patients. The primary endpoint of the trial was the normalization of the alanine aminotransferase level. Secondary end points included additional disease-related assessments, safety, and side effects. Sebelipase alfa was associated with a significantly higher rate of normalization of the alanine aminotransferase level, (the primary end point) than was placebo (31% vs. 7%, P = 0.03). In addition, sebelipase alfa was associated with significant improvement in six consecutive secondary end points, as compared with placebo. The decrease from baseline in the mean alanine aminotransferase level was significantly greater in the sebelipase alfa group than in the placebo group (−58 U per liter vs. −7 U per liter, P < 0.001). Similar results were seen with respect to normalization of the aspartate aminotransferase level (42% vs. 3%, P < 0.001; mean reduction from baseline, −42 U per liter vs. −6 U per liter; P < 0.001). An additional analysis of reduction in the alanine aminotransferase level with the use of recently applied criteria in studies of nonalcoholic fatty liver disease showed a response rate of 67% with sebelipase alfa versus 7% with placebo. The sebelipase alfa group had significantly greater mean percentage decreases from baseline in the LDL cholesterol level (difference from the change with placebo, −22.2 percentage points; P < 0.001), the non-HDL cholesterol level (difference from placebo, −21.1 percentage points; P < 0.001), and the triglyceride level (difference from placebo, −14.4 percentage points; P = 0.04) and a significantly greater mean percentage increase in the HDL cholesterol level (difference from placebo, 19.9 percentage points; P < 0.001). The number of patients with adverse events was similar in the two groups; most events were mild and were considered by the investigator to be unrelated to treatment. Sebelipase alfa therapy resulted in a reduction in multiple disease-related hepatic and lipid abnormalities in children and adults with lysosomal acid lipase deficiency.

Olipudase alfa-rpcp (Xenpozyme)

The efficacy of Xenpozyme for the treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) has been evaluated in 3 trials in patients with ASMD. 28 Trial 1 was a randomized, double-blinded, placebo-controlled, repeat-dose trial in 31 adult patients with ASMD (clinical diagnosis consistent with ASMD type B and A/B). Patients received either Xenpozyme or placebo. Key efficacy endpoints included assessment of % predicted diffusion capacity of the lungs for carbon monoxide (DLco), spleen volume, liver volume, and platelet count. At week 52, an increase of 20.9% in the mean percent change in % predicted DLco was observed in the Xenpozyme-treated patients compared to the placebo-treated patients (P = 0.0003). A reduction in spleen volume of 39.4% was observed in the Xenpozyme-treated patients compared to the placebo-treated patients (P < 0.0001). A 24.7% decrease in mean liver volume and a 15.6% increase in mean platelet count were also noted in the Xenpozyme-treated patients compared to the placebo-treated patients at week 52 (P < 0.0001 and P = 0.0280, respectively).28,31 Trial 2 was an open-label, repeated-dose trial of Xenpozyme in 8 pediatric

patients aged < 18 years with a clinical diagnosis consistent with ASMD type B and A/B. Exploratory efficacy endpoints related to organomegaly, pulmonary and liver functions, and linear growth were evaluated at week 52. Treatment with Xenpozyme resulted in improvements in mean percent change in % predicted DLco, spleen and liver volumes, platelet counts, and linear growth progression (as measured by height Z-scores) at week 52 as compared to baseline. Refer to the drug label for full results.28,32 Additionally, the 8 pediatric patients 2 to < 12 years of age from Trial 2 continued treatment in an open label long term trial (Trial 3) and were treated with Xenpozyme for 2.5 to 3.2 years. Efficacy analyses showed continued improvements in the 3 patients evaluated for % predicted DLco, 6 patients evaluated for platelet counts, and all 8 patients evaluated for spleen and liver volumes, compared to baseline, during the additional 6 months extension. In addition, the height Z-score increased by 1.3 from baseline when evaluated through 24 months of Xenpozyme treatment.

Avalglucosidase alfa-ngpt (Nexviazyme)

The efficacy and safety of avalglucosidase alfa-ngpt for the treatment of late onset Pompe disease was evaluated in a randomized, double-blinded, multinational, multicenter trial (NCT02782741). Efficacy and safety was compared to alglucosidase alfa. 100 treatment-naïve patients were randomized in a 1:1 ratio, based on forced vital capacity (FVC), age, gender, and country, to receive 20 mg/kg of avalglucosidase alfa-ngpt or alglucosidase alfa administered once every two weeks for 49 weeks. The trial included an open label, long-term, follow-up of up to 5 years, in which patients were switched to avalglucosidase alfa-ngpt treatment. The primary endpoint was the change in FVC (% predicted) in the upright position from baseline to week 49. Secondary endpoint was the change in total walking distance in 6 minutes (6-minute walk test) from baseline to week 49. At week 49, the least squares (LS) mean change in FVC was 2.9% (avalglucosidase alfa-ngpt) and 0.5% (alglucosidase alfa), with an estimated treatment difference of 2.4% (95% CI: -0.1, 5) favoring avalglucosidase alfa-ngpt (noninferiority margin of 1.1% [P = 0.0074], statistical superiority was not achieved [P = 0.06]). Secondary endpoint had an estimated treatment difference of 30 meters (95% CI: 1.3, 58.7) favoring avalglucosidase alfa-ngpt (P

HCPCS Code

HCPCS Code	Description	Dosage Form	Route of Administration
J0180	Agalsidase beta (Fabrazyme)	5 mg or 35 mg lyophilized cake/powder in single dose vial	intravenous
J0221	Alglucosidase alfa (Lumizyme)	5 mg/mL lyophilized powder for solution	Intravenous
J3385	Velaglucerase Alfa (VPRIV)	200 unit or 400 unit single dose vial	intravenous
J1786	Imiglucerase (Cerezyme)	400 units of lyophilized powder in single dose vial	Intravenous
J2840	Sebelipase alfa (Kanuma)	2 MG/1 ML solution in single dose vial	Intravenous
J0218	Olipudase alfa-rpcp (Xenpozyme)	20 mg of lyophilized powder in single dose vial	Intravenous
J0219	Avalglucosidase alfa-ngpt (Nexviazyme)	100 mg single-dose vial for reconstitution.	intravenous

Acronyms

NCD = National Coverage Determination

LCD = Local Coverage Determination

ERT = Enzyme Replacement Therapy

GAA = Acid alpha-glucosidase

GL-3 = Globotriaosylceramide

GD1 = Type 1 Gaucher disease

Gb3 = Globotriaosylceramide

rhLAL = Recombinant human lysosomal acid lipase

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