Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCEND082.0425	**ENDOCRINE & METABOLIC DRUGS** **ENZYME REPLACEMENT THERAPY** See Table 1 for Medications
Effective Date: 7/1/2025	**Review/Revised Date**: 10/23, 03/24, 10/24, 03/25 (JEF/MTW)
Original Effective Date: 08/23	**P&T Committee Meeting Date**: 06/23, 10/23, 04/24, 10/24, 04/25
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
For initiation of therapy (new starts to therapy) all the following criteria must be met:

1. Documentation of FDA-labeled indication (See Appendix 1) for the requested product
2. Dosing is within FDA-labeled guidelines (See Appendix 1).
3. For avalglucosidase alfa (Nexviazyme®) only: Patients weighing less than 30 kg must have a documented trial, failure, intolerance or contraindication to alglucosidase alfa (Lumizyme®)
4. For olipudase alfa (Xenpozyme®) only, the following additional criteria must be met:
    a. Clinical presentation must be consistent with acid sphingomyelinase deficiency (ASMD) type B OR ASMD type A/B
    b. Spleen volume of six multiples of normal (MN) or more for adults OR five MN or more for those less than 18 years old
    c. For adults only, diffusing capacity of the lungs for carbon monoxide (DLco) equal to 70% or less of predicted normal value
    d. The following are excluded from coverage:
        i. Use of invasive ventilatory support, or noninvasive ventilatory support while awake for greater than 12 hours a day

   ii. Acute or rapidly progressive neurological abnormalities and/or genotypes associated with ASMD type A, meaning homozygous for SMPD1 gene mutations R496L, L302P, and fs330 or any combination of these three mutations

5. For cerliponase alfa (Brineura®) only, the following additional criteria must be met:
   a. Diagnosis of neuronal ceroid lipofuscinosis type 2 (CLN2) confirmed by both of the following:
      i. Deficiency of tripeptidyl peptidase 1 (TPP1) enzyme activity (in a sample of leukocytes, fibroblasts, dried blood spot or saliva)
      ii. Genetic testing revealing one pathogenic mutation on each parental allele of TPP1/CLN2 gene
   b. Documentation of symptomatic disease (such as, seizures, changes in gait, falls, difficulty in ambulating, loss of language/delay in language development, visual failures)
   c. Baseline Motor Domain of the CLN2 Clinical Rating Scale score of at least one (See Appendix 2)
6. For velmanase alfa only, the following additional criteria must be met:
   a. Confirmed diagnosis of alpha-mannosidosis as defined by alpha-mannosidase activity less than 10% of normal activity in blood leukocytes
   b. Documented baseline serum oligosaccharide level
   c. Documented baseline value of either 6-minute walk test, 3-minute stair climb or forced vital capacity. Note: This may be waved for children under the age of three. Improvement or stabilization is required for reauthorization.
   d. Therapy is being used to treat non-central nervous system manifestations of alpha mannosidosis such as skeletal abnormalities, myopathy, motor function disturbances, immune deficiency
   e. No prior history of bone marrow transplant
7. For cipaglucosidase alfa-atga (Pombiliti®) only, the following additional criteria must be met:
   a. Documentation of baseline percent-predicted forced vital capacity (FVC) of 30% or higher than the predicted value for healthy adults
   b. Documentation of baseline 6-minute walk test (6MWT) of 75 meters or greater
8. For elapegademase-lvlr (Revcovi®) only, the following additional criteria must be met:
   a. A marked increase in the metabolite deoxyadenosine triphosphate (dATP) or total dAdo nucleotides [the sum of deoxyadenosine monophosphate (dAMP), deoxyadenosine diphosphate (dADP), and dATP] in erythrocytes
   b. Documentation showing that patient is not a candidate for or has failed a hematopoietic stem cell transplantation (HSCT)

i. May be approved as a “bridge” therapy before undergoing HSCT or an HSC-Gene Therapy clinical trial if a donor/ clinical trial has been identified (subject to policy coverage durations)

c. Documentation that patient does not have severe thrombocytopenia (platelet count less than 50,000 cells/microliter)

Note: If request is for a non-FDA approved dose, medical rational must be submitted in support of therapy with a higher dose for the intended diagnosis such as high-quality peer reviewed literature, accepted compendia or evidence-based practice guidelines and exceptions will be considered on a case-by-case basis.

For patients currently established on the requested therapy, all the following criteria must be met. Note: Medications obtained as samples, coupons, or any other method of obtaining medications outside of an established health plan benefit are NOT considered established on therapy.

1. Documentation of successful response to therapy (e.g., disease stability, improvement in symptoms or lack of decline compared to natural disease progression).
    a. For olipudase alfa (Xenpozyme®) only, documentation of improvement in at least one of the following: spleen volume, liver volume, platelet count, DLco or forced vital capacity (FVC)
    b. For cerliponase alfa (Brineura®) only, documentation of both of the following:
        i. No more than a 1-point decline in the Motor Domain of the CLN2 Clinical Rating Scale
        ii. Motor Domain of the CLN2 Clinical Rating Scale score remains above zero
    c. For velmanase alfa (Lamzede®) only, documentation of one of the following:
        i. For initial reauthorization: a decrease of serum oligosaccharides of 3 micromoles per liter or at least 30%
        ii. For subsequent reauthorizations: stabilization or improvement in either the 6-minute walk test, 3-minute stair climb or forced vital capacity
    d. For elapegademase-lvlr (Revcovi®) only, the following additional criteria must be met:
        i. Documentation of plasma target trough ADA activity of at least 30 mmol/hr/L in the past two months
        ii. Documentation of a trough erythrocyte dAXP level maintained below 0.02 mmol/L in the past six months
        iii. Documentation of immune function improvement (such as decrease in number of infections)

2. Dosing is within FDA-labeled guidelines

Note: If request is for a non-FDA approved dose, medical rational must be submitted in support of therapy with a higher dose for the intended diagnosis (such as high-quality peer reviewed literature, accepted compendia or evidence-based practice guidelines) and exceptions will be considered on a case-by-case basis.

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS:
Age must be appropriate based on FDA-approved indication

PRESCRIBER RESTRICTIONS:
Must be prescribed by or in consultation with a hepatologist, endocrinologist, medical geneticist, cardiologist, pulmonologist, neurologist, hematologist, oncologist, immunologist, or bone and mineral specialist

COVERAGE DURATION:
Initial authorization and reauthorization will be approved for one year.

QUANTITY LIMIT:
Initial dose approval will be based on patient's current weight (See Appendix 1). Increases in dose will require new authorization with patient's weight and relevant chart notes

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Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Enzyme replacement therapy is used to replace absent or defective enzymes. The most common conditions treated with enzyme replacement therapies are lysosomal storage diseases. Lysosomal storage diseases are genetically inherited rare

disorders caused by deficient activity of a distinct lysosomal enzyme. This results in accumulation of undegraded substrates leading to cellular and organ dysfunction. There are currently over fifty identified lysosomal storage diseases that affect various parts of the body with varying degrees of severity. Other treatment options for lysosomal storage diseases may include bone marrow transplant, gene therapy, substrate reduction therapy (for Gaucher disease), a pharmacologic chaperone (stabilizes and increases activity of a deficient enzyme in Fabry disease) and symptomatic treatments for the underlying disease.

Aldurazyme® (laronidase) is a recombinant form of human alpha-L-iduronidase. It provides exogenous enzymes for uptake into lysosomes and increase the catabolism of glycosaminoglycans (GAG). Laronidase uptake by cells into lysosomes is probably mediated by the mannose-6-phosphate receptors. Aldurazyme is approved for Mucopolysaccharidosis I (MPS I) and has been shown to improve pulmonary function (forced vital capacity) and walking capacity.

Elaprase® (idursulfase) is a purified form of human iduronate-2-sulfatase lysosomal enzyme. It provides an exogenous enzyme source to allow for catabolism of GAG in patients with Mucopolysaccharidosis II (MPS II) or Hunter Syndrome, where a deficiency of this enzyme results in GAG accumulation and subsequent organ dysfunction. Boxed warning includes higher incidence of hypersensitivity, serious adverse reactions, and antibody development in Hunter Syndrome patients aged seven years and younger with complete gene deletion, large gene rearrangement, nonsense, frameshift, or splice site mutations.

Mepsevii® (vestronidase alfa) is indicated for MPS VII, also known as Sly Syndrome. MPS VII is caused by mutations in the gene that encodes for beta-glucuronidase, located on chromosome 7q21.11. It is associated with significant soft tissue and skeletal abnormalities. A common presentation is hydrops fetalis. Heart disease and airway obstruction are major causes of death in people with MPS VII

Naglazyme® (galsulfase) is the first FDA approved treatment for patients with Mucopolysaccharidosis VI (MPS VI). Naglazyme® (galsulfase) is a hydrolytic lysosomal GAG-specific enzyme that decreases urinary GAG excretion and improves patient function and survival.

Vimizim® (elosulfase alfa) is the first FDA approved drug for Morquio A syndrome (MPS IVA), a rare autosomal recessive lysosomal storage disease. This condition results from the absence of the enzyme N-acetylgalactosamine-6-sultae sulfatase (GALNS) which normally clears out long chains of sugar molecules. About 800

people suffer from the disease in the U.S., with 3,000 patients in the developed world. Vimizim® is intended to provide the exogenous GALNS enzyme.

Black Box Warning for enzyme replacement therapies for MPS:
These agents contain boxed warning for risk of life-threatening anaphylactic reactions. Patients with compromised respiratory and/or cardiac function or acute respiratory and/or cardiac disease may be at risk of serious acute exacerbation due to infusion reactions. Appropriate medical support should be readily available when infusions of enzyme replacement therapies are administered.

Adzynma® (ADAMTS13, recombinant-krhn), is a human recombinant ADAMTS13 (A disintegrin and metalloproteinase with thrombospondin motifs 13) enzyme replacement therapy for prophylactic or on demand treatment of congenital (hereditary) thrombotic thrombocytopenic purpura (cTTP). ADAMTS13 enzyme is responsible for breaking down clotting protein von Willebrand factor into smaller units, thereby reducing platelet binding properties and propensity to form microthrombi. Prophylactic Adzynma therapy appears to result in fewer acute thrombotic thrombocytopenic purpura (TTP) events, subacute TTP events, and TTP manifestations compared with plasma-based therapies.

Cerezyme® (imiglucerase), Elelyso® (taliglucerase alfa) and Vpriv® (velaglucerase alfa) are all indicated for the treatment of Gaucher's Disease. Cerezyme® is a human enzyme beta-glucocerebrosidase analog which catalyzes the hydrolysis of the lipid glucocerebroside to glucose and ceramide which prevents its accumulation in macrophages. Elelyso™ is a hydrolytic lysosomal glucocerebroside-specific enzyme which catalyzes the hydrolysis of glucocerebroside to glucose and ceramide. In patients with type 1 Gaucher's disease, treatment with taliglucerase alfa reduced spleen and liver size, and stabilized hematologic parameters. Vpriv® is an enzyme created by gene activation technology in human fibroblast cells which catalyzes hydrolysis of glucocerebroside.

Fabrazyme® and Elfabrio® are used for patients with Fabry disease. These enzymes reduce globotriaosylceramide (GL-3) deposition in capillary endothelium of the kidney and certain other cell types. In adults, Elfabrio® was found to be non-inferior to Fabrazyme® in slowing kidney function decline. Elfabrio® has a longer half-life than Fabrazyme® and is currently being studied for every four-week dosing.

Kanuma® (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. In patients with lysosomal acid lipase (LAL) deficiency, replacement with sebelipase alfa, a recombinant form of LAL, results in improvement in disease-related hepatic and lipid parameters.

Lumizyme® (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). It contains a boxed warning for risk of life-threatening anaphylactic reactions and severe hypersensitivity have occurred during and after infusions. Immune-mediated reactions presenting as proteinuria, nephrotic syndrome, and necrotizing skin lesions have occurred in some patients following treatment. Therefore, patients need to be closely observed during and after administration. Patients must be informed about the signs and symptoms of anaphylaxis, hypersensitivity reactions, and immune-mediated reactions and be advised to seek immediate medical attention should signs/symptoms occur. Infantile-onset Pompe disease patients with compromised cardiac or respiratory function may be at risk of serious exacerbation due to fluid overload and require additional monitoring.

Nexviazyme® (avalglucosidase alfa-ngpt) also provides an exogenous source of GAA for patients with Pompe disease. It carries similar warnings and precautions as Alglucosidase alfa.

Pombiliti® (cipaglucosidase alfa-atga) also provides an exogenous source of GAA for patients with late-onset Pompe disease. It carries similar warnings and precautions as alglucosidase alfa and avalglucosidase alfa.

Xenpozyme® (olipudase alfa) provides an exogenous source of the enzyme acid sphingomyelinase (ASM), the enzyme that is deficient in acid-sphingomyelinase deficiency (ASMD). Olipudase alfa degrades sphingomyelin to ceramide and phosphocholine. Olipudase alfa is not expected to cross the blood-brain barrier or alter CNS manifestations of ASMD.[18,22,23]

Velmanase alfa-tycv (Lamzede®) provides an exogenous source of alpha-mannosidase. Velmanase alfa binds to extracellular mannose-6-phosphate receptors on the cell surface and is transported into lysosomes where it exerts enzyme activity. Alpha-mannosidase catalyzes the degradation of accumulated mannose-containing oligosaccharides. Velmanase alfa is not expected to cross the blood-brain barrier or alter CNS manifestations of alpha-mannosidosis[1,29].

Cerliponase alfa, a proenzyme, is taken up by target cells in the central nervous system and is translocated to the lysosomes through the Cation Independent

Mannose-6-Phosphate Receptor (CI-MPR, also known as M6P/IGF2 receptor). Cerliponase alfa is activated in the lysosome and cleaves from the N-terminus of proteins to minimize accumulation of lysosomal storage materials.

FDA APPROVED INDICATIONS: See Appendix 1

POSITION STATEMENT:
Mucopolysaccharidoses (MPS) is a group of inherited diseases in which a defective or absence of an enzyme causes large amounts of complex sugar molecules to accumulate in harmful amounts in the body's cells and tissues. This accumulation causes permanent, progressive cellular damage that affects appearance, physical abilities, organ and system function, and in most cases, mental development.

There are distinct types and subtypes of MPS. Deficiencies are in the following enzymes:

MPS I (Hurler – most severe form, Hurler-Scheie – intermediate, Scheie – least severe form): alpha-L-iduronidase
MPS II (Hunter syndrome): iduronate sulfatase
MPS IIIA: heparan N-sulfatase
MPS IIIB: alpha-N-acetylglucosaminidase
MPS IIIC: acetyl-CoA:alpha-glucosaminide acetyltransferase
MPS IIID: N-acetylglucosamine 6-sulfatase
MPS IV (Morquio syndrome): N-acetylgalactosamine 6-sulfatase (Type A) or beta-galactosidase (Type B)
MPS VI (Maroteaux-Lamy syndrome): N-acetylgalactosamine 4-sulfatase
MPS VII (Sly syndrome): beta-glucuronidase

Clinical examination and urine tests (excess mucopolysaccharides are excreted in the urine) are the first steps in the diagnosis of an MPS disease but enzyme assays testing a variety of cells or blood in culture for enzyme deficiency or genetic testing are used to provide definitive diagnosis of one of the mucopolysaccharidoses. Urine glycosaminoglycan (GAG) concentrations vary based on age and are subject to dilution effects so may not be a reliable confirmatory measure.

Gaucher disease (GD) is an inborn error of metabolism in which deficiency of the enzyme glucocerebrosidase results in the glycolipid glucocerebroside, throughout the body especially within the bone marrow, spleen and liver. There are different presentations (types) of Gaucher disease, and the symptoms and physical findings can vary greatly with some patients being asymptomatic with others suffering serious consequences. Enzyme replacement therapy (ERT) in patients with non-

neuronopathic Gaucher disease Type 1 is usually reserved for patients with clinically significant manifestations of the disease.

Fabry Disease is an X-linked genetic disorder caused by a mutation in lysosomal enzyme alpha-galactosidase A leading to a buildup of globotriaosylceramide, or Gb3, which is an intermediate metabolite of globoside, a major glycosphingolipid. Gb3 is suspected to have cytotoxic, proinflammatory, and profibrotic effects and classical presentation of the disease often involves renal and cardiac dysfunction, neuropathies, and gastrointestinal symptoms. Both males and females can have varying symptoms and severity of the disease.

Pegunigalsidase alfa (Elfabrio®) may have a favorable immunogenicity profile over agalsidase beta as the proportion of patients with neutralizing anti-drug antibodies declined over time with pegunigalsidase alfa but not with agalsidase beta (Fabrazyme®) in BALANCE trial[37]. Evidence from one published phase 1/2 trial that pegunigalsidase alfa reduces the number of renal Gb3 inclusions (a surrogate marker) in adult patients with Fabry disease not currently on enzyme replacement therapy. Prespecified noninferiority margin was met in one unpublished phase 3 trial comparing pegunigalsidase alfa to agalsidase beta. The median eGFR slope in the pegunigalsidase alfa arm was -2.514 mL/min/1.73 m2/year and -2.155 mL/min/1.73 m2/year in the agalsidase beta arm. Migalastat (Galafold®) is currently approved under accelerated approval for only patients with an amenable mutation (~30% of those with Fabry disease).

Lysosomal acid lipase deficiency (LALD) is a metabolic storage disease that includes Wolman disease (early-onset, severe) and Cholesteryl ester storage disease ([CESD] late-onset, less severe). LALD is caused by mutations in the LIPA gene, which provides instructions to produce the lysosomal acid lipase enzyme. When there is not enough of this enzyme, the body cannot break down certain fats and this leads to a toxic buildup of fatty substances in the body's cells and tissues.

Rapidly Progressive LAL Deficiency Presenting within the First 6 Months of Life (Wolman disease)
A multicenter, open-label, single-arm clinical study of sebelipase alfa was conducted in nine infants with LAL deficiency who had growth failure or other evidence of rapidly progressive disease prior to six months of age. The age range at entry was one to six months. Patients received sebelipase alfa at 0.35 mg/kg once weekly for the first two weeks and then 1 mg/kg once weekly. Due to suboptimal clinical response, doses in all six surviving patients were escalated to 3 mg/kg once weekly, between four and 88 weeks (median 11 weeks) after starting treatment at 1 mg/kg. In one patient, the dose was escalated to 5 mg/kg once weekly at Week 88 due to decreased growth velocity in a setting of positive neutralizing anti-drug antibodies to

sebelipase alfa. The recommended dosage for these patients is 1 mg/kg to 3 mg/kg once weekly.

Efficacy of sebelipase alfa was assessed by comparing the survival of nine sebelipase alfa-treated patients at 12 months of age with an untreated historical cohort of 21 patients with a similar age at disease presentation and clinical characteristics. Of the nine sebelipase alfa-treated infants, six patients survived beyond 12 months of age, compared to 0 of 21 patients in the historical cohort, all of whom died by eight months of age. The median age of the six surviving sebelipase alfa-treated patients was 18.1 months (range 12 to 42.2 months). Following initiation of treatment with sebelipase alfa 1 mg/kg once weekly, weight-for-age z-scores improved in three of five surviving patients with growth failure, and all six surviving patients demonstrated improvements in weight-for-age z-scores following dose escalation to 3 mg/kg once weekly.

Pediatric and Adult Patients with LAL Deficiency (Cholesteryl ester storage disease)
The safety and efficacy of sebelipase alfa were assessed in 66 pediatric and adult patients with LAL deficiency, aged four to 58 years (71% were less than 18 years old), in a multicenter, double-blind, placebo-controlled trial. Patients were randomized to receive sebelipase alfa at a dosage of 1 mg/kg (n=36) or placebo (n=30) once every other week for 20 weeks in the double-blind period. Sixty-two of the 66 (94%) patients had LDL-c of 130 mg/dL or greater at study entry. The majority of patients (58%) had LDL-c above 190 mg/dL at study entry, and 24% of patients with LDL-c above 190 mg/dL remained on lipid lowering medications. At the completion of the 20-week double-blind period of the trial, a statistically significant improvement in percent change from baseline in LDL-c was observed in the sebelipase alfa-treated group as compared to the placebo group (mean difference and 95% C.I.: -22%, [-33%, -15%]; p<0.0001). LDL-c of less than 130 mg/dL was achieved in 13 of 32 (41%; 95% C.I.: [24%, 58%]) sebelipase alfa-treated patients and in only two of 30 (7%; 95% C.I.: [0%, 16%]) placebo-treated patients with baseline LDL-c of 130 mg/dL or greater. A statistically significant improvement in percent change from baseline at 20 weeks was also observed in the sebelipase alfa-treated group, compared to the placebo group for other parameters related to LAL deficiency, including decreases in non-HDL-c (mean difference and 95% C.I.: -21%, [-30%, -15%]; p<0.0001) and triglycerides (mean difference and 95% C.I.: -14%, [-28%, -1%]; p=0.0375), and increases in HDL-c (mean difference and 95% C.I.: 20%, [12%, 26%]; p<0.0001). The effect of sebelipase alfa on cardiovascular morbidity and mortality has not been established.

Patients treated with sebelipase alfa had larger reductions from baseline in ALT values and liver fat content (measured by MRI), compared to patients treated with

placebo. The significance of these findings as they relate to progression of liver disease in LAL deficiency has not been established.

Open-label Extension
Pediatric and adult patients who participated in the randomized, placebo-controlled trial were eligible to continue treatment in an open-label extension. Sixty-five of 66 patients (98%) entered the open-label period in which all patients received sebelipase alfa at a dosage of 1 mg/kg once every other week. During the open-label extension, patients treated with sebelipase alfa for up to 36 weeks demonstrated improvements in lipid parameters, including LDL-c and HDL-c levels, and ALT.

Pompe Disease is a rare condition with three available enzyme therapies approved for treatment alglucosidase alfa (Lumizyme®), avalglucosidase alfa (Nexviazyme®), and cipaglucosidase alfa-atga (Pombiliti®). Previously, alglucosidase alfa was also available as Myozyme® but it is no longer available in the U.S.

Myozyme® (alglucosidase alfa) has been used in the treatment of infantile-onset Pompe disease in open-label clinical trials, resulting in improvements in ventilator-free survival compared to untreated historical controls in one trial and no improvements in survival versus untreated historical controls in another trial. The safety and efficacy of Lumizyme® (alglucosidase alfa) was assessed in one 18 month pivotal, randomized, double-blind, placebo-controlled, multicenter study in 90 patients with late onset Pompe disease. Lumizyme-treated patients had an increase in the distance walked on 6-minute walk test (6MWT) as well as an increase in the predicted forced vital capacity (FVC). For patients treated with Lumizyme®, the mean increase in 6MWT was 25.1 meters (average baseline 332.2 meters); the placebo group experienced a 3.0-meter (average baseline 317.9 meters) reduction in 6MWT distance (P = 0.03, for the difference). The estimated change in FVC expressed as a percentage of each patients predicted value, was an increase of 1.2 percentage points for the patients treated with Lumizyme® and a decrease of 2.2 percentage points for the patients who received placebo (P = 0.006, for the difference).

Avalglucosidase alfa (Nexviazyme®, alglucosidase alfa (Lumizyme®), and cipaglucosidase alfa-atga (Pombiliti®) are structurally and mechanistically similar. Nexviazyme® was designed to increase cellular uptake of the enzyme through a 15-fold increase in M6P content compared to Lumizyme®, the clinical implications of this have not been demonstrated in clinical trials. In the Phase 3 COMET trial, Nexviazyme® was found to be noninferior to Lumizyme® and did not meet the threshold for superiority. In addition, patients previously treated with Lumizyme® were excluded from the COMET trial. The safety and efficacy of cipaglucosidase alfa-atga (Pombiliti®) was established in the PROPEL trial comparing

cipaglucosidase alfa/miglustat to alglucosidase alfa/placebo in adult patients with late-onset Pompe disease (LOPD). Both patients who were ERT-naive as well as those who had received prior ERT (alglucosidase alfa at its recommended dose for >2 years) were eligible for participation. After 52 weeks the combination of cipaglucosidase/miglustat did not improve the primary endpoint of the mean change in 6-minute walk distance compared to alglucosidase/placebo; however, did achieve a statistically significant improvement in the secondary outcome measure of percent predicted forced vital capacity. Pre-specified analyses showed that patients who were previously treated with enzyme replacement therapy and switched to cipaglucosidase alfa/miglustat showed favorable results compared with patients who were enzyme replacement therapy naïve.

Acid-sphingomyelinase deficiency (ASMD) is an autosomal recessive lysosomal disease caused by mutations in the *SMPD1* gene. It is also known as ASM-deficient Niemann-Pick disease. The enzyme acid sphingomyelinase metabolizes sphingomyelin into ceramide and phosphocholine. A deficiency in ASM leads to accumulation of sphingomyelin in organ systems such as liver, spleen, lymph nodes, adrenal cortex, lung airways, bone marrow and central nervous system (CNS). There is a spectrum of disease with ASMD ranging from severe (Type A) to milder form (Type B). Individuals with ASMD Type A experience hepatosplenomegaly, pathologic changes to the lungs in infancy and severe CNS involvement. ASMD Type A is a fatal neurodegenerative disease that presents in infancy and individuals rarely survive beyond two to three years of age. Individuals with ASMD Type B have less severe disease and little to no CNS involvement with most having later onset of symptoms and can survive into adulthood. Individuals with AMSD Type A/B can have vastly different disease presentation and progression rate but all have some CNS manifestation. Prior to olipudase alfa, treatment was supportive therapy. [18,19] Olipudase alfa is not expected to treat CNS manifestations of ASMD as it does not cross the blood brain barrier.[1,18]

Olipudase alfa was studied in adults (ASCEND) and pediatrics (ASCEND-Peds) with ASMD type B or type A/B. No individuals with ASMD type A were enrolled in the trials. Key inclusion criteria included spleen volume ≥6 multiples of normal (MN) measured by MRI or ≥5 MN for patients less than 18 years old and for adults only, diffusing capacity of the lungs for carbon monoxide (DLco) equal to 70% or less of predicted normal value. Individuals with acute or rapidly progressive neurological abnormalities and/or genotypes associated with ASMD type A as well as those dependent on ventilatory support were excluded from the trials.
Olipudase alfa showed improvement in the primary efficacy endpoint spleen volume and in the ASCEND trial, diffusing capacity of the lung (DLco). Improvements in other key endpoints, liver volume and platelet count, were also observed.

CLN2 is a rare (0.22 to 9 per 100,000 live births), autosomal recessive neurodegenerative disorder caused by mutations in the TPP1/CLN2 gene and the resulting TPP1 enzyme deficiency. With TPP1 enzyme deficiency, there is accumulation of ceroid and neuronal loss. Presentation is often with seizures and ataxia, usually at age 2-4 (late-infantile onset).

The expert recommended gold standard for diagnosis of CLN2 is deficient TPP1 enzyme activity (in leukocytes, fibroblasts, or dried blood spots) in the setting of normal activity of a control enzyme such as palmitoyl-protein thioesterase 1 (PPT1) and/or β-galactosidase and the identification of causative mutations in each allele of the TPP1/CLN2 gene. Alternatively, if this is not possible to obtain both analyses, CLN2 can be diagnosed with demonstration of either:

- Deficient TPP1 enzyme activity in leukocytes or fibroblasts
- Detection of two pathogenic mutations in trans of the TPP1/CLN2 gene.

Cerliponase alfa was studied in a single arm, Phase I/II, open-label, dose escalation (initial dose of 30-300 mg every 14 days, then 300 mg every 14 days) 48-week clinical trial. Patients (N=24 treated, N=42 in historical control) aged 3-15 years with confirmed diagnosis of early to moderate CLN2 with TPP1 activity (dried blood spot) and CLN2 genotype analysis were enrolled in the trial. Early to moderate disease was defined as a score 3-5 on adapted two domain CLN2 disease rating scale, including a score of at least one in each domain. The CLN2 Clinical Rating Scale has a Motor and Language domain, each with a 0 to 3 score (the highest possible combined score is 6). However, only the Motor domain was used to assess disease progression in clinical studies. Decline was defined as a sustained 2-point loss or unreversed score of 0 in the Motor domain of the CLN2 Clinical Rating Scale. Of note, patients with previous stem cell, gene therapy, or enzyme replacement therapy for CLN2 disease were excluded from the trial. The primary endpoint was the response rate (defined as the absence of an unreversed two-point decline or score of zero in the CLN2 score) at 48 weeks, separately assessed as matched controls based on age and motor function. 87% (20/23) of treated patients responded to treatment at week 48 and 96 compared to the expected response rate of 50% from the historical control group (P-value=0.0002). All patients treated with cerliponase alfa had less than 2-point reduction in the motor and language domains compared to 43% of matched historical controls (P-value <0.001). This trial was limited by the small sample size due to rarity of condition and inconsistent treatment regimens.

Alpha-mannosidosis (AM) is a very rare (prevalence 1 in 500 000) lysosomal storage disorder that results from reduced activity of the enzyme alpha-mannosidase, caused by gene variants in the *MAN2B1* gene, resulting in progressive accumulation of mannose-rich oligosaccharides in various organs and

tissues. There is a spectrum of disease with AM ranging from mild (Type 1) to severe form (Type 3). Symptoms vary widely in type and severity. Symptoms can include immunodeficiency (recurrent infections), facial and skeletal abnormalities, hearing impairment, impairment of speech, intellectual disability, muscular weakness, joint abnormalities and ataxia. Prior to velmanase alfa, treatment was primarily with supportive therapy. Varying success has been seen with bone marrow transplant in patients with AM.[31,33] Velmanase alfa is not expected to treat CNS manifestations of AM as it does not cross the blood brain barrier.[1,31]

Velmanase alfa was studied in a 52-week double blind placebo-controlled phase 3 trial. Twenty-five patients aged 6-35 years of age were enrolled. Individuals with a history of bone marrow transplant were excluded from the trial. The trial's primary endpoints were change in baseline serum oligosaccharides and 3-minute stair climb test. Change in serum oligosaccharides was statistically significantly reduced at 52 weeks. Absolute change from baseline in serum oligosaccharides was -3.5 µmol/L (-4.4, -2.6) $p<0.001$. The other primary endpoint, 3-minute stair climbing test as well as the secondary endpoints, forced vital capacity and 6-minute walk test, were not statistically significant but favored velmanase alfa.[32]

Congenital (hereditary) thrombotic thrombocytopenic purpura (cTTP) is a very rare thrombotic disorder caused by severe deficiency of the von Willebrand factor cleaving protease ADAMTS13. Severe deficiency of ADAMTS13 leads to accumulation of ultra-large von Willebrand factor (VWF) multimers with high platelet binding activity. This can result in spontaneous formation of microthrombi and ischemic damage to multiple organs.[42] Replacement of ADAMTS13 through acute or regular prophylactic infusions of plasma-based therapies has been the standard of care. Compared to ADAMTS13, recombinant (Adzynma), plasma-based therapies can contain variable amounts of ADAMTS13. They can cause hypersensitivity and have the potential risk of transmission of infectious agents.

ADAMTS13, recombinant (Adzynma) was studied in a randomized, controlled, open-label, crossover Phase 3 trial. This trial showed that prophylactic Adzynma may decrease the incidence of acute TTP events, subacute TTP events and TTP manifestations compared to plasma-based therapy (standard of care) in patients with cTTP. Due to low number of acute and subacute events, only descriptive statistics were performed on acute events (primary outcome) and subacute events.

- No acute events occurred in patients receiving Adzynma; 1 event occurred in patients receiving plasma-based therapies
- Two patients receiving Adzynma had a subacute event in the single arm period 3; 5 subacute events occurred in four patients receiving plasma-based therapies

- Incidence of TTP manifestations (such as thrombocytopenia events or microangiopathic hemolytic anemia events) was lower with Adzynma than plasma-based therapies
- On-demand treatment: all six acute TTP events resolved after treatment with either Adzynma or plasma-based therapies
- Mean time above 10% ADAMTS13 activity and mean average ADAMTS13 activity were ~ 3 to 4-fold higher with Adzynma than standard of care
- Mean time ADAMTS13 activity remained above 10% was 5.3 days with Adzynma vs 1.6 days with standard of care

Adenosine deaminase severe combined immune deficiency (ADA-SCID):
ADA_SCID is a rare genetic disorder with an overall incidence of 1 in 200,000 to 1 in 1,000,000 live births throughout the world. Without a functional adenosine deaminase enzyme, there is an intracellular accumulation of adenosine and deoxyadenosine (dAXP). This leads to severe combined immunodeficiency with dysfunction of T, B, and natural killer cells. Defects due to build of adenosine and dAXP can also be seen in the lungs, brain, skeleton, liver, and kidneys

- The consensus approach for the management of ADA-SCID in the Journal of Allergy and Clinical Immunology in 2019 recommends that all patients diagnosed with ADA-SCID should initially receive enzyme replacement therapy (ERT), followed by definitive treatment with allogeneic hematopoietic stem cell transplantation (HSCT) or autologous hematopoietic stem cell gene therapy (HSC-GT). Ideally, in most patients ERT should be used as “bridge” for relatively short periods (a few months to approximately 2 years) before undergoing HSCT or HSC-GT. Treatment with ERT can serve as an immediate stabilizing measure and can help restore immune function. It may even help to improve hepatocellular abnormalities, pulmonary alveolar proteinosis, and bone dysplasia associated with untreated ADA deficiency
- Revcovi® (elapegademase-lvlr):
  - Can be self-administered after patient or caregiver is trained and demonstrates proficiency at preparation of the injection and administration.
  - Use of elapegademase should be monitored by measuring trough plasma ADA activity, trough dAXP levels, and/or total lymphocyte counts.
    - Trough plasma ADA activity (pre-injection) should be measured every two weeks for PEGylated bovine ADA-naïve patients and every four weeks for patients previously receiving PEGylated bovine ADA therapy, during the first eight to 12 weeks of treatment, and every three to six months thereafter.
    - Monitoring labs include erythrocyte dAXP, drawn two months after starting elapegademase treatment, while trough erythrocyte dAXP

levels should be maintained below 0.02 mmol/L and monitored at least twice a year. The degree f immune function may vary from patient to patient. Each patient will require appropriate monitoring consistent with immunologic status.

- Total and subset lymphocytes should be monitored periodically as follows:
  - PEGylated bovine ADA-naïve patients: every four to eight weeks for up to one year, and every three to six months thereafter
  - Other patients: every three – six months

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Table 1: BILLING GUIDELINES AND CODING

HCPCS code	Code Description	Brand Name
J7171	Injection, ADAMTS13, recombinant-krhn, 10 units	**Adzynma**
J1931	Injection, laronidase, 0.1mg	**Aldurazyme®**
J0567	injection, cerliponase alfa, 1mg	**Brineura®**
J1786	Injection, imiglucerase, 10 units	**Cerezyme®**
J1743	Injection, idursulfase, 1mg	**Elaprase®**
J3060	Injection, taliglucerase alfa, 10 units	**Elelyso®**
J2508	Injection, pegunigalsidase alfa-iwxj, 20 mg	**Elfabrio®**
J0180	Injection, agalsidase beta, 1 mg	**Fabrazyme®**
J2840	Injection, sebelipase alfa, 1mg	**Kanuma®**
J0217	Injection, velmanase alfa, 10 mg	**Lamzede®**
J0221	Injection, alglucosidase alfa (Lumizyme), 10mg	**Lumizyme®**
J3397	Injection, vestronidase alpha-vjbk, 10 mg	**Mepsevii®**
J1458	Injection, galsulfase, 1mg	**Naglazyme®**
J0219	Injection, avalglucosidase alfa-ngpt, 10 mg	**Nexviazyme®**
J1203	Injection, cipaglucosidase alfa-atga, 5 mg	**Pombiliti®**
C9399 J3590 (NOC codes)	Injection, elapegademase-lvlr, 2.4 mg	**Revcovi®**
J1322	Injection, elosulfase alfa, 1mg	**Vimizim®**
J3385	Injection, velaglucerase alfa, 100 units	**Vpriv®**
J0218	Injection, olipudase alfa, 20 mg	**Xenpozyme®**
ADMINISTRATION◊		
96365	Ther/proph/diag iv inf init	
96366	Ther/proph/diag iv inf addon	
96372	Ther/proph/diag inj sc/im	
96374	Ther/proph/diag inj iv push	
96379	Ther/Prop/Diag Inj/Inf Proc	
96413	Chemo iv infusion 1 hr	
96415	Chemo iv infusion addl hr	

MODIFIERS		
-JW	Drug Amount Discarded/Not Administered to Any Patient	

◊ Coding/Administration Notes:

• The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.

• HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as “medically unlikely edits” (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

PHARMACY PRIOR AUTHORIZATION POLICY AND STEP THERAPY CRITERIA ORPTCEND	ENDOCRINE & METABOLIC DRUGS ENZYME REPLACEMENT THERAPY See Table 1 for Medications

Appendix 1.

Drug name Generic (Brand®)	**Indication**	**Confirmatory Tests**	**Symptoms**	**Dosing schedule**	**How Supplied**
Laronidase (Aldurazyme®)	MPS I (Hurler, Hurler-Scheie forms as well as Scheie [only those with moderate to severe symptoms with this form])	• Molecular genetic testing of mutation in the alpha-L-iduronidase (*IDUA)* gene • Deficiency or absence of fibroblast or leukocyte enzyme activity of alpha-L-iduronidase	Developmental delay, severe coarse facies, hepatosplenomegaly, airway obstruction, joint disease, corneal clouding, aortic valve disease	0.58 mg/kg IV every week	2.9mg/5ml vial
Idursulfase (Elaprase®)	MPS II (Hunter syndrome) For 16 months and older	• Deficiency in iduronate 2-sulfatase (IDS) activity as measured in fibroblasts/leukocytes combined with normal enzyme activity level of another sulfatase • Molecular genetic testing for deletion or mutations in the *IDS* gene (Xq28) Also known as: ID2S, MPS2, SIDS	Abnormal facial features, macrocephaly, hepatosplenomegaly, cardiovascular disorders, neurocognitive decline, deafness	0.5 mg/kg IV every week	6mg/3ml vial

PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCEND082	ENDOCRINE & METABOLIC DRUGS ENZYME REPLACEMENT THERAPY See Table 1 for Medications

Drug name Generic (Brand®)	**Indication**	**Confirmatory Tests**	**Symptoms**	**Dosing schedule**	**How Supplied**
Vestronidase alpha-vjbk (Mepsevii®)	MPS VII (Sly Syndrome)	• Leukocyte or fibroblast glucuronidase enzyme assay or genetic testing. Urinary glycosaminoglycan (uGAG) excretion at a minimum of 3-fold over the mean normal for age • Molecular genetic testing of mutations in the *GUSB* gene	Variable from very sever to attenuated: Hydrops fetalis (fluid retention throughout body) in severe cases, slower height growth, slow cognitive development by 1-3 years with regression of skills until death, coarse facial features, respiratory weakness, thick lips/enlarged tongue, valvular heart disease, enlarged liver/spleen, skeletal malformation	4 mg/kg IV every two weeks	10 mg/5 mL vial
Galsulfase (Naglazyme®)	MPS VI (Maroteaux-Lamy syndrome)	• Absence or deficiency of fibroblast or leukocyte enzyme activity of N-acetylgalactosamine 4-sulfatase (arylsulfatase) • Molecular genetic confirmation of mutations in the *ARSB* gene (5q13-q14). Gene also known as: *ASB, G4S, MPS6*	Coarse facial features, severe skeletal disease, joint abnormalities, respiratory disease, cardiac abnormalities, obstructive sleep apnea, pulmonary hypertension	1mg/kg IV every week	5mg/5ml vial

PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCEND082	ENDOCRINE & METABOLIC DRUGS ENZYME REPLACEMENT THERAPY See Table 1 for Medications

Drug name Generic (Brand®)	Indication	Confirmatory Tests	Symptoms	Dosing schedule	How Supplied
Elosulfase alfa (Vimizim®)	MPS IVA (Morquio A syndrome) For ages 5 years and older	• Absence or deficiency of fibroblast or leukocyte GALNS enzyme activity • Molecular genetic testing for mutations in the *GALNS* gene (16q24.3). Gene also known as: *GALNAC6S, GAS, GalN6S, MPS4A*	Skeletal disease, short stature, corneal opacities, ligamentous laxity	2mg/kg IV every week	5mg/5ml vial
Imiglucerase (Cerezyme®)	Gaucher Disease Type 1 For ages 2 years and older	• Biochemical assay of beta-glucocerebrosidase activity (in leukocytes or skin fibroblasts) of less than 30% of normal values • DNA testing shows a mutation in the *GBA* gene. Also known as: GBA1, GCB, GLUC, GBA	Hepatosplenomegaly, anemia, thrombocytopenia, skeletal abnormalities, lung disease	2.5 units/kg 3 times per week, up to 60 units/kg every 2 weeks For Type 3 (off-label): doses up to 120 units/kg every 2 weeks have been safely administered	400 Units per vial
Taliglucerase alfa (Elelyso®)	Gaucher Disease Type 1	• Biochemical assay of beta-glucocerebrosidase	Hepatosplenomegaly, anemia, thrombocytopenia, skeletal abnormalities, lung disease	60 Units/kg IV every other week	200 Units per vial

Drug name Generic (Brand®)	Indication	Confirmatory Tests	Symptoms	Dosing schedule	How Supplied
	For ages 4 years and older	activity (in leukocytes or skin fibroblasts) of less than 30% of normal values • DNA testing shows a mutation in the *GBA* gene. Also known as: GBA1, GCB, GLUC, GBA		Patients switching from imiglucerase: Begin at the same unit/kg dose as the patient's previous imiglucerase dose	
Velaglucerase alfa (Vpriv®)	Gaucher Disease Type 1 For ages 4 years and older	• Biochemical assay of beta-glucocerebrosidase activity (in leukocytes or skin fibroblasts) of less than 30% of normal values • DNA testing shows a mutation in the *GBA* gene. Also known as: GBA1, GCB, GLUC, GBA	Hepatosplenomegaly, anemia, thrombocytopenia, skeletal abnormalities, lung disease	60 Units/kg IV every other week Patients switching from imiglucerase (on a stable dose): start treatment with previous imiglucerase dosage two weeks after the last imiglucerase dose	400 Units per vial
Agalsidase beta (Fabrazyme®)	Fabry disease For ages 2 years and older	• Absence or deficiency (<1%) of alpha-galactosidase activity in leukocytes, dried	Acroparesthesias, anhidrosis or hypohidrosis, angiokeratomas, corneal dystrophy, renal dysfunction and heart manifestations	1 mg/kg IV every 2 weeks	35 mg vial 5 mg vial

Drug name Generic (Brand®)	Indication	Confirmatory Tests	Symptoms	Dosing schedule	How Supplied
		blood spots, or serum analysis ○ For biological males only ○ Often included in male newborn screening • Molecular genetic testing for deletion or mutations in galactosidase alpha (*GLA)* gene, also known as *GALA*	Other symptoms: chronic fatigue, dizziness, headache, generalized weakness, nausea, and/or vomiting, delayed puberty, lack of or sparse hair growth, and rarely malformation of the joints of the fingers.		
Pegunigalsidase alfa (Elfabrio®)	Fabry disease For ages 18 years and older	• Absence or deficiency (<1%) of alpha-galactosidase activity in leukocytes, dried blood spots, or serum analysis ○ For biological males only ○ Often included in male newborn screening • Molecular genetic testing for deletion or	Acroparesthesias, anhidrosis or hypohidrosis, angiokeratomas, corneal dystrophy, renal dysfunction and heart manifestations Other symptoms: chronic fatigue, dizziness, headache, generalized weakness, nausea, and/or vomiting, delayed puberty, lack of or sparse hair growth, and rarely malformation of the joints of the fingers.	1 mg/kg every 2 weeks	20 mg/10 mL vial 5mg/2.5 mL vial

Drug name Generic (Brand®)	Indication	Confirmatory Tests	Symptoms	Dosing schedule	How Supplied
		mutations in galactosidase alpha (*GLA)* gene, also known as *GALA*			
Sebelipase alfa (Kanuma®)	Lysosomal acid lipase deficiency (Wolman Disease)	• Absence or deficiency of lysosomal acid lipase activity by dried blood spot test • Molecular genetic testing for deletion or mutation of the lipase A, lysosomal acid type (*LIPA*) gene	Abdominal distention, hepatosplenomegaly, liver fibrosis, ascites, malabsorption, steatorrhea, hernia, hypotonia, delays in motor skill development, adrenal gland calcification, anemia.	Rapidly progressive LAL deficiency presenting within first 6 months of age: 1 mg/kg/dose once weekly; may increase to 3 mg/kg IV every week; for patients with continued suboptimal clinical response may increase to 5mg/kg IV once weekly Pediatric and adults: 1 mg/kg IV every two weeks; may increase to 3 mg/kg IV every week	20 mg/10mL vial
Alglucosidase alfa (Lumizyme®)	Pompe disease (infantile or late-onset)	• Absence or deficiency of acid alpha-glucosidase (GAA)	Respiratory distress, skeletal muscle weakness, cardiac hypertrophy	20mg/kg IV every 2 weeks	50 mg vial

Drug name Generic (Brand®)	Indication	Confirmatory Tests	Symptoms	Dosing schedule	How Supplied
	[acid α-glucosidase (GAA) deficiency]	activity in blood, muscle or skin fibroblast • Molecular genetic testing for deletion or mutations in *GAA* Gene also known as *LYAG*			
Avalglucosidase alfa (Nexviazyme®)	Patients 1 year of age and older with late-onset Pompe disease (not currently approved for infantile. It is currently being studied in this population)	Same as Lumizyme®	Same as Lumizyme®	≥30 kg: 20 mg/kg every 2 weeks <30 kg: 40 mg/kg every 2 weeks	100 mg vial
cipaglucosidase alfa-atga (Pombiliti®)	Adult patients with late-onset Pompe disease in combination with Opfolda® (miglustat) who are not improving on current ERT	Same as Lumizyme®	Same as Lumizyme®	<40kg: do not use ≥40kg: 20 mg/kg IV every other week 1-3 hours after oral administration of Opfolda®	105 mg vial

PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCEND082	ENDOCRINE & METABOLIC DRUGS ENZYME REPLACEMENT THERAPY See Table 1 for Medications

Drug name Generic (Brand®)	**Indication**	**Confirmatory Tests**	**Symptoms**	**Dosing schedule**	**How Supplied**
Olipudase alfa (Xenpozyme®)	Acid-sphingomyelinase deficiency (ASMD) – treatment of non-CNS manifestations	• Genetic testing for mutation in the sphingomyelin phophodiesterase-1 (*SMPD1*) gene • Reduced AMS activity in peripheral blood leukocytes or cultured skin fibroblasts[20]	Type B or A/B: hepatosplenomegaly, thrombocytopenia, interstitial lung disease, short stature, delayed skeletal maturation, hyperlipidemia Type A: feeding difficulties, loss of early motor skills, interstitial lung disease withing first few months of life, profound loss of neurological function, hepatosplenomegaly	Maintenance dose of 3 mg/kg IV every 2 weeks Specific dose escalation regimens for pediatrics and adults	20 mg vial **4 mg vial**
Cerliponase alfa injection (Brineura®)	Slow the loss of ambulation in pediatric patients with neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency	Deficiency of tripeptidyl peptidase 1 (TPP1) enzyme activity (in a sample of leukocytes, fibroblasts, dried blood spot or saliva) AND Genetic testing revealing one pathogenic mutation on each parental allele of TPP1/CLN2 gene	seizures, changes in gait, falls, difficulty in ambulating, loss of language/delay in language development, visual failures	300 mg IV once every other week	150 mg/5ml vial
Velmanase alfa (Lamzede®)	Alpha-mannosidosis (AM) – treatment	• Alpha-mannosidase activity less than 10%	Symptoms vary widely in type and severity. Symptoms can include immunodeficiency (recurrent infections), facial and skeletal	1 mg/kg (actual body weight) IV once weekly	10 mg vial

Drug name Generic (Brand®)	Indication	Confirmatory Tests	Symptoms	Dosing schedule	How Supplied
	of non-CNS manifestations	of normal activity in blood leukocytes • Genetic testing revealing biallelic pathogenic variants in *MAN2B1* There is no clear relationship between genotype and severity of disease.	abnormalities, hearing impairment, impairment of speech, intellectual disability, muscular weakness, joint abnormalities, ataxia. Mild form (type 1): usually recognized after age ten with slow disease progression Moderate form (type 2): Usually recognized before age ten with slow disease progression Severe form (type 3): usually begins within first year of life with rapid disease progression		
ADAMTS13, recombinant-krhn (Adzynma®)	Congenital (hereditary) thrombotic thrombocytopenic purpura (cTTP) Not indicated for acquired, immune-mediated TTP (aTTP or iTTP)	• ADAMTS13 activity level below 10% • Genetic testing showing biallelic pathogenic variants in ADAMTS13 Individuals with cTTP will not have ADAMTS13 autoantibodies. Individuals with iTTP/aTTP will have ADAMTS13 autoantibodies.	Lethargy, abdominal discomfort, headache, loss of concentration, neurologic abnormalities, organ ischemia, kidney dysfunction, thrombocytopenia, and microangiopathic hemolytic anemia (MAHA) Acute event: thrombocytopenia, MAHA, variable degree of ischemic organ damage, particularly affecting the brain, heart, and kidney	Prophylactic therapy: 40 units/kg IV once every other week (may go to weekly) On-demand: day 1: 40 units/kg IV day 2: 20 units/kg IV day 3+: 15 units/kg IV daily until 2 days after acute event	500 unit 1500 unit

PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCEND082	ENDOCRINE & METABOLIC DRUGS ENZYME REPLACEMENT THERAPY See Table 1 for Medications

Drug name Generic (Brand®)	**Indication**	**Confirmatory Tests**	**Symptoms**	**Dosing schedule**	**How Supplied**
Elapegademase-lvlr (Revcovi®)	Adenosine deaminase severe combined immune deficiency (ADA-SCID) in adult and pediatric patients	One of the following: • Mutation in the ADA gene by molecular genetic testing • Deficient ADA catalytic activity (less than 1% of normal) in hemolysates (in untransfused individuals) or in extracts of other cells (such as, blood mononuclear cells, fibroblasts)	Life-threatening infections (commonly in the lungs, GI tract, skin), chronic persistent diarrhea, failure to thrive in the first months of life. Also prolonged hyperbilirubinemia, hepatitis, Omenn syndrome (maculopapular rash that becomes desquamative, acute necrotizing hepatitis with jaundice, interstitial pneumonitis, and massive diarrhea).	Starting dose determined by whether or not the patient has had prior treatment with PEGylated bovine ADA: • For patients transitioning from PEGylated bovine ADA to elapegademase: 0.2 mg/kg weekly, intramuscularly (dose may also be calculated using a conversion formula provided in the drug label). • For PEGylated bovine ADA -naïve patients: 0.4 mg/kg weekly based on ideal body weight or actual body weight (whichever is greater), divided into two doses	2.4 mg vial

PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCEND082	ENDOCRINE & METABOLIC DRUGS ENZYME REPLACEMENT THERAPY See Table 1 for Medications

Drug name Generic (Brand®)	**Indication**	**Confirmatory Tests**	**Symptoms**	**Dosing schedule**	**How Supplied**
				(0.2 mg/kg twice a week), intramuscularly	

Appendix 2: CLN2 Clinical Rating Scale (Motor Domain)

MOTOR FUNCTION[1,3]		
3	**Normal***	Grossly normal gait. No prominent ataxia, no pathologic falls.
2	**Abnormal**	Independent gait, as defined by ability to walk without support for 10 steps. Will have obvious instability, and may have intermittent falls.
1	**No unaided walking**	Requires assistance to walk, or can crawl only.
0	**Immobile**	Can no longer walk or crawl.

Decline was defined as a sustained (unreversed) 2-point loss or an unreversed score of 0 in the Motor domain of the CLN2 Clinical Rating Scale

Adapted from: Steinfeld R, et al. *Am J Med Genet*. 2002:112:347-354.