Lysosomal Storage Disorders Medical Drug Criteria Program Summary

POLICY REVIEW CYCLE

Effective Date **Date of Origin**
01-01-2025

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Aldurazyme® (laronidase) Injection for intravenous use	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 Limitations of Use: - The risks and benefits of treating mildly affected patients with the Scheie form have not been established. - Aldurazyme has not been evaluated for effects on the central nervous system manifestations of the disorder.		1
Cerezyme® (imiglucerase) Injection for intravenous use	Treatment of adults and pediatric patients 2 years of age and older with Type 1 Gaucher disease that results in one or more of the following conditions: anemia, thrombocytopenia, bone disease, hepatomegaly or splenomegaly		2
Elaprase® (idursulfase) Injection for intravenous use	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. Safety and efficacy of Elaprase have not been established in pediatric patients less than 16 months of age.		3
Elelyso® (taliglucerase alfa) Injection for intravenous use	For the treatment of patients 4 years and older with a confirmed diagnosis of Type 1 Gaucher disease		4
Elfabrio®	Treatment of adults with confirmed Fabry disease		58

Agent(s)	FDA Indication(s)	Notes	Ref#
(pegunigalsidase alfa-iwxj) Intravenous injection			
Fabrazyme® (agalsidase beta) Injection for intravenous use	For the treatment of adult and pediatric patients 2 years of age and older with confirmed Fabry disease	.	5
Kanuma® (sebelipase alfa) Injection for intravenous use	Treatment of patients with a diagnosis of Lysosomal Acid Lipase (LAL) deficiency		6
Lumizyme® (alglucosidase alfa) Injection for intravenous use	For patients with Pompe disease (acid alpha-glucosidase [GAA] deficiency)		7
Mepsevii® (vestronidase alfa-vjbk) Injection for intravenous use	Pediatric and adult patients for the treatment of Mucopolysaccharidosis VII (MPS VII, Sly syndrome) Limitations of Use: - The effect of Mepsevii on the central nervous system manifestations of MPS VII has not been determined.		8
Naglazyme® (galsulfase) Injection for intravenous use	For patients with Mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy syndrome) Naglazyme has been shown to improve walking and stair-climbing capacity.		9
Nexviazyme® (avalglucosidase alfa-ngpt) Injection for intravenous use	Treatment of patients 1 year of age and older with late-onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency)		53

Agent(s)	FDA Indication(s)	Notes	Ref#
Pombiliti™ (cipaglucosidase alfa-atga) Injection for intravenous use	Treatment of adult patients with late-onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency) weighing greater than or equal to 40 kg and who are not improving on their current enzyme replacement therapy (ERT); Pombiliti (a hydrolytic lysosomal glycogen-specific enzyme) is indicated in combination with Opfolda (an enzyme stabilizer)		59
Vimizim® (elosulfase alfa) Injection for intravenous use	For patients with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome)		10
Vpriv® (velaglucerase alfa) Injection for intravenous use	For long-term enzyme replacement therapy (ERT) for patients with type 1 Gaucher disease	The efficacy and safety of Vpriv has not been established in pediatric patients younger than 4 years of age	11
Xenpozyme® (olipudase alfa-rpcp) Injection for intravenous use	Treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) in adult and pediatric patients		54

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Inborn Errors of Metabolism	Congenital metabolic disorders result from the absence or abnormality of an enzyme or its cofactor, leading to either accumulation or deficiency of a specific metabolite. There is a traditional classification system for inborn errors of metabolism (IEM) grouping the disorders according to the general type of metabolism involved (e.g., amino acid disorders, fatty acid oxidation disorders, lysosomal storage disorders, peroxisomal disorders, urea cycle disorders). The IEM grouping of lysosomal storage disorders will be further discussed here.
Lysosomal Storage Disorders	Lysosomal storage disorders (LSDs) are caused by defective lysosomal metabolism that results in the accumulation of various macromolecules such as mucopolysaccharides, sphingolipids, and glycoproteins.(13) Progressive accumulation of these materials in organs and tissues results in distension of the cell, disruption of cellular function, and organ failure. The majority of these disorders have substantial neurological involvement with developmental regression, seizures, and learning difficulties. Most patients affected by these disorders have a decreased life expectancy with considerable morbidity. LSDs are believed to have a combined prevalence of around 1 in every 5,000 births. There is no cure or definitive treatment available for any LSD. Enzyme replacement therapy (ERT) is available for some LSDs and is generally considered safe.(14)

	LSDs can be subdivided according to the involved compound or pathway. Four of these subgroups – sphingolipidoses, mucopolysaccharidoses, lysosomal acid lipase deficiency, and glycogen storage disorder – will be discussed here.
Sphingolipidoses	**Fabry Disease** Fabry disease, also called Anderson-Fabry disease, is a rare X-linked error of the glycosphingolipid metabolic pathway caused by pathogenic mutations in the *GLA* (galactosidase alpha) gene, resulting in functional deficiency of the enzyme alpha-galactosidase A (alpha-Gal A).(16) Markedly reduced, or absent, activity of alpha-Gal A results in progressive accumulation of glycolipids, primarily globotriaosylceramide (GL-3, Gb3), within lysosomes in multiple cell types throughout the body.(16,17) This includes those particularly relevant to disease pathology (e.g., vascular endothelial cells, podocytes, cardiomyocytes, arterial smooth muscle cells) and other cell types in the kidneys, nervous system, and other organs.(17,18) Although some *GLA* variants do not appear to cause disease, more than a thousand disease-causing *GLA* variants have been identified. The severity of symptoms may vary among individuals depending upon the specific *GLA* mutation within their family. In general, mutations that result in little to no alpha-Gal A activity cause the classic Fabry phenotype, and those mutations that result in residual alpha-Gal A activity cause the atypical later-onset phenotype.(16,17) The "classic" form of Fabry disease is the most severe clinical phenotype and occurs predominantly in males. These patients are characterized by absent or severely reduced alpha-Gal A activity, with childhood or adolescent onset of symptoms including severe neuropathic or limb pain, abdominal pain, telangiectasias and angiokeratomas, corneal opacities, renal involvement that may progress to end-stage renal disease (ESRD), and hearing loss, with cardiac and cerebrovascular involvement occurring by adulthood. The spectrum of disease severity in heterozygous female patients ranges from asymptomatic to a severe phenotype resembling the male "classic" phenotype and is, in part, dependent on the mutation and the X chromosome inactivation (Lyonization) profile. The prevalence of signs and symptoms at any given age is lower in females, though increasing age will result in development of cardiac and cerebrovascular involvement.(17,18) Fabry disease should be suspected in patients with a family history of Fabry disease or those who present with the clinical manifestations or laboratory abnormalities associated with the disease. The diagnosis is typically confirmed by biochemical and/or molecular genetic testing, with the latter approach being the final determinant.(17) An initial evaluation includes baseline documentation of renal function (e.g., proteinuria, glomerular filtration rate [GFR]), cardiac function (e.g., left ventricular hypertrophy, conduction defects, mitral and/or aortic valve abnormalities), ophthalmological signs (e.g., corneal verticillate, subcapsular cataracts, conjunctival and/or retinal vasculopathy), peripheral nerve symptoms (e.g., neuropathic pain, heat and/or cold intolerance, impaired sweat function), and gastrointestinal involvement (e.g., nausea, vomiting, abdominal pain, diarrhea, constipation).(17,18) After a thorough clinical evaluation, mutational analysis of the *GLA* gene is the gold-standard assay to confirm the diagnosis of Fabry disease in males and females. For male patients suspected of having Fabry disease, an initial measurement of alpha-Gal A activity (in leukocytes, plasma, fibroblasts, or dried blood spots [DBS]) may be performed. However, the alpha-Gal A activity assay is not definitive confirmation of Fabry disease, since the assay will identify less than 50% of female carriers. Additionally, for patients with residual alpha-Gal A activity on assay (3-35%), genetic testing for a pathogenic *GLA* gene will confirm the Fabry disease diagnosis, and establish the patient's amenability to treatment with chaperone therapy.(17) There is no cure for Fabry disease. Intravenous enzyme replacement therapy (ERT) with Fabrazyme (agalsidase beta), which focuses on replacing the missing or deficient enzyme (alpha-Gal A), had been the only treatment for Fabry disease. However, in August 2018 the FDA approved migalastat, an oral capsule taken every other day, as first-line therapy in patients with amenable *GLA* gene variants.(16,18) Migalastat is a pharmacologic chaperone that binds to and stabilizes specific (amenable) mutant

	forms of alpha-Gal A, thereby facilitating proper trafficking of the enzyme to lysosomes. Once in the lysosome, migalastat dissociates from alpha-Gal A allowing it to then catabolize accumulated glycolipids.(16) Patients on ERT or migalastat should have a clinical evaluation every 6-12 months. Renal function, cardiac function, ophthalmological signs, peripheral nerve symptoms, and gastrointestinal involvement should all be assessed to monitor disease manifestations, disease severity, and/or side effects of therapy.(17) **Gaucher Disease** Gaucher disease (GD), the most common of the lysosomal storage disorders (LSDs), is a rare autosomal recessive metabolic disorder affecting only 1 in 40,000 in the general United States population.(22) Mutations in the *GBA* (glucocerebrosidase) gene cause reduced activity of the lysosomal enzyme glucocerebrosidase (also known as acid beta-glucosidase), resulting in the accumulation of harmful quantities of the glycolipid glucocerebroside (also known as glucosylceramide, or GLC) and other related sphingolipids. This multisystemic accumulation of GLC in various tissues, especially in lysosomes of macrophages, compromises the bone marrow, spleen, and liver, and less often the lungs, skin, kidneys, and heart.(19,22,24,51,52) GD is classified into 3 clinical types, distinguished by their clinical features, management, and prognosis. However, as with most genetic diseases, there is a continuum of clinical findings and overlap within and between types, resulting in identification of additional subtypes.(22,23,51) GD Type 1 (GD1) is distinguished from GD Types 2 (GD2) and 3 (GD3) by the lack of characteristic involvement of the central nervous system (CNS).(19,22,23,24) As such, it is also known as non-neuronopathic GD.(19,22) In the United States, Europe, and Israel, 90% of GD patients have GD1, with a high carrier frequency in the Ashkenazi-Jewish population.(19,22,23,24) Age of onset for GD1 is variable, with some patients presenting between 12 and 24 months of age and others having no clinical signs until late adulthood.(19,22) Manifestation in the first or second decades of life typically results in more aggressive and severe symptoms than those manifesting at a later stage of life.(22) Presentation of symptoms among patients with GD1 is variable. Splenomegaly is the most common symptom; hepatomegaly is also common, but the liver increases relatively less than the spleen. Other common presenting symptoms are anemia, thrombocytopenia, bone disease, and delayed growth.(19,22,23,24,52) GD2 is an acute neuronopathic form of GD characterized by early onset, typically in the first year after birth. Neurologic complications are extensive and severe, with limited psychomotor development. Death occurs within the first 2 years of life, usually due to respiratory failure.(19,22,23) GD3 is the subacute or chronic neuronopathic form, has later onset than GD2, and has slower disease progression with patients typically surviving to second or third decades of life. The distinction between GD2 and GD3 is difficult.(19) A diagnosis of GD should be considered in patients with unexplained anemia and easy bruising, particularly if they have enlargement of the spleen and liver.(19) Definitive diagnosis of GD can be confirmed by the finding of reduced glucocerebrosidase activity in leukocytes, fibroblasts, or other nucleated cells.(19,22,23,51,52) This enzyme assay test is typically known as BGL (beta-glucosidase leukocyte), and a finding of 15% or less of mean normal glucocerebrosidase enzyme activity is indicative of GD.(23) If BGL results are not conclusive and/or further confirmatory testing is desired, genetic testing is an option. Identification of two pathogenic alleles in the *GBA* gene can also determine diagnosis of GD.(19,23,51) The presence of neurologic complications has critical implications for prognosis and treatment and should be determined as soon as possible after diagnosis. Neuronopathic symptoms indicative of GD2 and GD3 include bulbar signs (e.g., stridor, strabismus, swallowing difficulty), pyramidal signs (e.g., opisthotonus, head retroflexion, spasticity, trismus), oculomotor apraxia, tonic-clonic

	seizures, myoclonic epilepsy, dementia, and ataxia. If not already performed as part of the diagnostic process, baseline measurement of hemoglobin level, platelet count, liver volume, and spleen volume should be documented.(22,23,52) When possible, management of a patient with GD should occur with a multidisciplinary team at a Comprehensive Gaucher Treatment Center(23) (list of facilities nationwide available at www.gaucherdisease.org). Goals of treatment are elimination or improvement of symptoms, prevention of irreversible complications, and improvement in overall health and quality of life. An additional goal in children is optimization of growth.(19,24) Currently, two different therapeutic approaches for the treatment of GD1 are used: enzyme replacement therapy (ERT) [Cerezyme (imiglucerase), Vpriv (velaglucerase alfa), Elelyso (taliglucerase alfa)] and substrate reduction therapy (SRT) [Cerdelga (eliglustat), Zavesca (miglustat)].(19,23,24,51) ERT, intravenously administered, targets macrophages and increases the breakdown of accumulated glycolipids.(24) SRT, orally administered, reduces the amount of synthesized GLC to a level that can be effectively cleared by the mutated enzyme's residual activity.(23,24) The decision to offer ERT or SRT in patients with GD1 is based upon disease severity and/or significant disease progression.(22,24,52) To begin treatment with ERT or SRT, clinically significant manifestations must be present. Thrombocytopenia of sufficient magnitude to justify initiation of treatment is defined by platelet counts less than 100,000 microliter, as well as symptomatic presentation of splenomegaly, anemia, bone disease, and/or delayed growth.(19,22,23,24,51) **Niemann-Pick Disease** Acid sphingomyelinase deficiency (ASMD) is a rare, progressive, lysosomal storage disease that is caused by a mutation in the *SMPD1* (sphingomyelin phosphodiesterase-1) gene, which causes a deficiency of the enzyme acid sphingomyelinase. ASMD is historically known as Niemann-Pick disease types A, A/B, B. Niemann-Pick type C is now considered a separate disorder, distinct from types A, A/B, and B; it does not involve a deficient enzyme. As such, ASMD is also known as acid-sphingomyelinase-deficient Niemann-Pick disease. ASMD has an estimated incidence of 0.4 to 0.6 per 250,000 births worldwide.(55,56) ASMD is a disease spectrum which has traditionally been broken down into two subgroups - neuronopathic (type A) and non-neuronopathic (type B). Type A generally causes severe neurodegenerative disease during infancy, while type B is generally not considered to be a neurologic disease. However, since ASMD is a disease spectrum with cases falling between these two extremes, type A/B can be used to refer to intermediate forms, which can include those that have type B with neurological findings.(55,56) The most common presenting symptom in NPD-A is hepatosplenomegaly, usually detectable by age three months; over time the liver and spleen become massive in size. Psychomotor development progresses no further than the 12-month level, after which neurologic deterioration is relentless. Failure to thrive typically becomes evident by the second year of life. A classic cherry-red spot of the macula of the retina, which may not be present in the first few months, is eventually present in all affected children. Interstitial lung disease caused by storage of sphingomyelin in pulmonary macrophages results in frequent respiratory infections and often respiratory failure. Most children succumb before the third year of life. NPD-B generally presents later than NPD-A, and the manifestations are less severe. NPD-B is characterized by progressive hepatosplenomegaly, gradual deterioration in liver and pulmonary function, osteopenia, and atherogenic lipid profile. No central nervous system (CNS) manifestations occur. Individuals with NPD-A/B have symptoms that are intermediate between NPD-A and NPD-B. The presentation in individuals with NPD-A/B varies

	greatly, although all are characterized by the presence of some CNS manifestations. Survival to adulthood can occur in individuals with NPD-B and NPD-A/B.(55) Diagnosis of ASMD is established by detection of biallelic pathogenic variants in *SMPD1* and/or residual acid sphingomyelinase enzyme activity that is less than 10% of controls (in peripheral blood lymphocytes or cultured skin fibroblasts).(55,56). Management for ASMD is supportive care directed at treatment of manifestations. Enzyme therapy replacement with olipudase alfa has demonstrated improvement in respiratory function (improved diffusion capacity of the lungs for carbon monoxide [DLco]), reduction in spleen volume, reduction in liver volume, and an increase in mean platelet count. Clinical trial participants had a diffusion capacity of the lungs for carbon monoxide (DLco) less than or equal to 70% of the predicted normal, as well as enlarged spleen volume.(54)
Mucopolysaccharidoses	The mucopolysaccharidoses (MPS) are LSDs caused by the deficiency of enzymes required for the breakdown of glycosaminoglycans (GAGs). The accumulation of GAGs in lysosomes of various organs and tissues results in cellular dysfunction and clinical abnormalities. The MPS are rare conditions, with an estimated total incidence of 1 in 20,000 live births, and all are autosomal recessive disorders, with the exception of MPS II which is X-linked. Seven different types of MPS have been identified and are differentiated biochemically by their associated enzyme deficiency.(25) Five of the seven types – MPS I, II, IV, VI, VII – will be discussed here. **Mucopolysaccharidosis Type I (MPS I) – Hurler, Hurler-Scheie, and Scheie Syndromes** MPS I is a rare, chronic, progressive LSD caused by a mutation in the alpha-L-iduronidase (*IDUA*) gene, which regulates production of the enzyme alpha-L-iduronidase. Deficient levels of functional alpha-L-iduronidase results in an inability of the lysosome to catabolize certain GAGs – namely dermatan sulfate and heparan sulfate – which then progressively accumulate in the lysosome, interfering with proper cell functioning and ultimately leading to progressive damage of tissues and organs.(25,28) Individuals with MPS I were previously classified as having either a severe form (Hurler syndrome) of the disease, intermediate form (Hurler-Scheie syndrome), or mild form (Scheie syndrome). Although the term Hurler syndrome is still used, the term attenuated MPS I is now used in place of Hurler-Scheie and Scheie.(25,28) Hurler syndrome, the severe form of MPS I, is characterized by impaired cognitive development, progressive coarsening of facial features, hepatosplenomegaly, respiratory failure, cardiac valvulopathy, recurrent otitis media, corneal clouding, musculoskeletal manifestations such as joint stiffness and contractures, and dysostosis multiplex. The average age at death is five years, and nearly all patients die before 10 years.(25) A key difference between severe and attenuated phenotypes is that attenuated patients do not show early developmental delay and do not experience progressive decline in mental capabilities. As a group, attenuated patients show significant variability in the symptoms they have and the rate of progression. Some children are mildly affected and have a near normal lifespan, while others develop symptoms during childhood, usually around 6 or 7 years old, and can develop life-threatening complications by their teen-aged years or during their 20s. The symptoms of the attenuated form are as described above for the severe form. The symptoms can be as significant as the severe form, or can be milder.(28) A diagnosis of MPS I is based upon identification of characteristic symptoms, a detailed patient and family history, a thorough clinical evaluation, and a variety of specialized tests. Confirmation of disease requires demonstration of a deficiency (less than 10% of average reference values) of alpha-L-iduronidase enzyme activity in leukocytes, fibroblasts, plasma, or serum. Dried blood spot screening is also a valuable diagnostic

	method. Molecular genetic analysis can detect *IDUA* gene mutations but is available as a diagnostic service only at specialized laboratories. Any diagnostic test should be reviewed by a professional with experience in lysosomal diseases, since the assays are complex and the results often difficult to interpret.(28,29) Treatment options for MPS I include symptom-based care, hematopoietic stem cell transplantation (HSCT), and enzyme replacement therapy (ERT) with laronidase (Aldurazyme).(25,28,29,30) HSCT's main indication is for patients with the severe form of MPS I, because – if performed before two years of age – it seems to favorably and significantly alter their cognitive impairment.(25,30) ERT therapy with laronidase has demonstrated decreased hepatomegaly, improved respiratory function (improvement in the predicted normal forced vital capacity [FVC]), improved walking ability (in the six-minute walk test [6MWT]), increased joint range of motion, decreased left ventricular hypertrophy, decreased sleep apnea and hypopnea episodes, improved growth (height and weight), and decreased urinary GAG excretion.(25,29,30) Patients eligible for therapy with laronidase should have a deficiency in alpha-L-iduronidase activity, or genetic analysis confirming *IDUA* gene mutation, or both. For patients with the severe and intermediate forms of MPS I (Hurler, Hurler-Scheie), better outcomes can be achieved with immediate ERT treatment upon confirmation of diagnosis.(57) For patients with the mild form of MPS I (Scheie), ERT treatment is indicated once moderate-to-severe symptoms present. Clinical MPS I manifestations known to respond to ERT: respiratory diseases (e.g., upper airway obstructions such as sleep apnea/hyperpnea syndrome, recurrent infection, restrictive and interstitial respiratory diseases); osteoarticular disorders which compromise mobility and independence in activities of daily living; cardiac disorders (e.g., cardiomyopathy, cor pulmonale, valve disease).(25,29,57) **Mucopolysaccharidosis Type II (MPS II) – Hunter Syndrome** MPS II, or Hunter syndrome, is an X-linked disorder caused by a mutation in the iduronate-2-sulfatase (*IDS*) gene, resulting in deficiency of the lysosomal enzyme iduronate-2-sulfatase. Deficient levels of this enzyme results in accumulation of GAGs such as heparan and dermatan sulfate.(25,26) Hunter syndrome occurs as part of a wide clinical spectrum, traditionally categorized into a severe form and a mild/attenuated form based on the age at onset of signs and symptoms, the presence or absence of neurological involvement, and length of survival. The severe or neuropathic form is characterized by upper respiratory tract dysfunctions, sleep apnea, joint stiffness, pelvic dysplasia, vertebral and rib abnormalities, dysostosis multiplex, hepatomegaly (with or without splenomegaly), recurrent otitis media, hearing loss, dental abnormalities, skin disorders, and ocular abnormalities. In addition, cardiologic manifestations are common and are usually observed around 5 years of age, generally constituting the primary cause of death. From a neurological point of view, about two thirds of Hunter syndrome patients present with manifestations such as developmental delay and/or neurologic regression. These findings indicate the presence of the neuropathic form of the disease. More severely affected patients may experience seizures and/or behavioral changes, such as hyperactivity, aggressiveness, and obstinacy. The attenuated non-neuropathic form of Hunter syndrome is characterized by little or no central nervous system involvement, with preserved intelligence and an extended life expectancy.(25,26) Confirmation of disease occurs with biochemical and/or genetic analysis. Biochemical confirmation of Hunter syndrome is demonstrated by a deficiency of iduronate-2-sulfatase enzyme activity in leukocytes, fibroblasts, or plasma. Dry blood spot screening is also a valuable diagnostic method.(25) Demonstration of normal activity of a different sulfatase enzyme is required to rule out multiple sulfatase deficiency. Multiple sulfatase deficiency is a rare autosomal recessive disorder caused by deficiency of all lysosomal sulfatase enzymes, and patients present with a variable combination of features of MPS II and MPS VI.(48,49) Molecular genetic analysis can

	detect *IDS* gene mutations and is important for genetic counseling. Any diagnostic test should be reviewed by a professional with experience in lysosomal diseases, since the assays are complex and the results often difficult to interpret.(25) The treatment of MPS II is typically recommended only with the enzyme replacement therapy idursulfase (Elaprase). Stem cell transplantation has shown limited clinical benefit and carries a high risk of morbidity and mortality.(25,26) ERT therapy with idursulfase has demonstrated decreased hepatosplenomegaly, improved respiratory function (improvement in the predicted normal forced vital capacity [FVC]), improved walking ability (in the six-minute walk test [6MWT]), increased joint range of motion, improved cardiac outcomes, improved growth (height and weight), and decreased urinary GAG excretion.(25,26,31) Guidelines in the past have indicated ERT only for those with symptomatic involvement and without severe cognitive impairment.(25) However, updated guidelines recommend that ERT should be initiated as early as possible for all patients with a biochemically confirmed diagnosis of MPS II, regardless of overt symptomatic involvement. (26,31) The benefit of early intervention with ERT is supported by data from recent studies.(31) Guidelines agree that the benefits of idursulfase are questionable in patients with severe impairment of cognitive function, since the treatment does not cross the blood-brain barrier.(25,26,31) However, European and Latin American guidelines agree that the decision to initiate treatment in this population should be at the clinician's discretion in discussion with the child's parents. An expert panel consensus noted that all symptomatic patients in whom there is an expectation that ERT will alter the course of the somatic involvement are candidates for a trial (12-18 months) of ERT, even if cognitive impairment is already evident. Continuation of therapy requires clinical improvement or stabilization of patient's condition.(26,31) **Mucopolysaccharidosis Type IV (MPS IV) – Morquio Syndrome** MPS IV, also known as Morquio syndrome, exists in two forms: IVA and IVB, the former of which will be further discussed here. Morquio A syndrome is caused by a mutation in the galactosamine (N-acetyl)-6-sulfatase (*GALNS*) gene, resulting in a deficiency of the enzyme *N*-acetylgalactosamine-6-sulfatase. Deficient levels of this enzyme results in accumulation of the GAGs keratan sulfate and chondroitin-6-sulfatase in cell lysosomes which leads to tissues and organ dysfunction.(32,45) Morquio A syndrome is a chronic progressive disease with multisystem involvement. The specific disease manifestations depend grossly on the residual *N*-acetylgalactosamine-6-sulfatase activity and the accumulation rate and location of storage material in tissues. Infants usually appear normal at birth, but progressively develop profound skeletal and joint abnormalities (generally more extensive and severe than other MPS disorders), and an array of non-skeletal manifestations including respiratory disease, cardiac disease, impaired vision, hearing loss, dental problems, and to a lesser extent hepatomegaly. Morquio A can be distinguished from other types of MPS disorders by the presence of short-trunk dwarfism with short neck, hypermobility of joints, and lack of cognitive impairment.(32,45) Diagnosis is confirmed by deficiency of *N*-acetylgalactosamine-6-sulfatase activity in leukocytes or fibroblasts. Molecular genetic analysis can detect *GALNS* gene mutations, and is a further confirmation of the diagnosis.(32,45) Elosulfase alfa (Vimizim) is currently the only FDA approved agent to treat Morquio A syndrome. Historically only palliative care was available, since experience with stem cell transplantation is limited and lacks efficacy. International guidelines indicate that treatment with elosulfase alfa should be implemented as soon as the diagnosis of Morquio A syndrome has been confirmed, to replace the deficient *N*-acetylgalactosamine-6-sulfatase enzyme and to help prevent irreversible damage.

	Studies have demonstrated improvements in the six-minute walk test (6MWT) and forced vital capacity (FVC).(32,45) **Mucopolysaccharidosis Type VI (MPS VI) – Maroteaux-Lamy Syndrome** MPS VI, also known as Maroteaux-Lamy syndrome, is caused by a mutation in the arylsulfatase B (*ARSB*) gene, resulting in the deficiency of lysosomal enzyme *N*-acetylgalactosamine-4-sulfatase (arylsulfatase B). Deficient levels of this enzyme result in the accumulation of dermatan sulfate which causes apoptosis of chondrocytes and ensuing progressive arthropathy.(33) Severely affected children present at ages one to six years with coarse facial features, severe skeletal disease, joint abnormalities, respiratory disease, and cardiac abnormalities. Obstructive sleep apnea, pulmonary hypertension, and corneal clouding can occur. Intelligence is usually normal, although vision and hearing disorders can lead to developmental delay.(25,33) Diagnosis is confirmed by reduced arylsulfatase B enzyme activity (less than 10% of the lower limit of normal) in cultured fibroblasts or isolated leukocytes.(33) Demonstration of normal activity of a different sulfatase enzyme is required to rule out multiple sulfatase deficiency. Multiple sulfatase deficiency is a rare autosomal recessive disorder caused by deficiency of all lysosomal sulfatase enzymes, and patients present with a variable combination of features of MPS II and MPS VI.(50) Molecular genetic analysis can further confirm the diagnosis through detection of *ARSB* gene mutations but is available only at specialized laboratories.(33,34) Historically, supportive therapies and stem cell transplant were the only therapies available for MPS VI patients. Enzyme replacement therapy with galsulfase (Naglazyme) is recommended for all patients with a confirmed diagnosis, and has demonstrated improved endurance (as measured by six-minute walk test [6MWT], and stair-climbing), respiratory function improvements (increase in forced vital capacity [FVC]), and reduction in urinary GAG levels. Results show that, when initiated early, galsulfase improves growth velocity and prevents progression of cardiac abnormalities. Findings also suggest a trend for improvement in bone disease, spleen and liver size, facial dysmorphia, and joint mobility. Continuation of therapy requires clinical improvement or stabilization of the patient's condition.(25,33) **Mucopolysaccharidosis Type VII (MPS VII) – Sly Syndrome** MPS VII, also known as Sly syndrome, is caused by mutations in the gene encoding beta-glucuronidase (*GUSB*). The enzyme deficiency results in accumulation of the GAGs heparan sulfate, dermatan sulfate, chondroitin-4-sulfate, and chrondroitin-6-sulfate.(35,36) Clinical features and complications are variable, but all have short stature due to growth retardation and skeletal abnormalities, dysostosis multiplex, and some degree of intellectual disability. Hydrops fetalis is a common presentation and may account for a large proportion of patients not being diagnosed due to death before a diagnosis can be made. Other manifestations include hepatosplenomegaly, macrocephaly, and respiratory dysfunction.(35,36) Diagnosis is supported by X-ray evidence of dysostosis multiplex and increased levels of urinary GAGs. Diagnosis is confirmed by demonstration of beta-glucuronidase deficiency in cultured leukocytes and fibroblasts.(36,37) Molecular genetic analysis for mutations in the *GUSB* gene is also available.(35) Prenatal diagnosis is possible

	through amniocentesis or chorionic villus sampling, by molecular analysis or measurement of enzyme activity in trophoblasts or amniocytes.(35,37) In 2017 the enzyme replacement therapy (ERT) vestronidase alfa-vjbk (Mepsevii) was approved to treat pediatric and adult patients with MPS VII. There are currently no global treatment guidelines available for MPS VII; however it is argued that ERT should be initiated as early as possible following diagnosis, including before the onset of clinical disease, in order to obtain better long-term treatment outcomes.(36) Clinical studies demonstrate benefits such as decreased hepatosplenomegaly, improved respiratory function (forced vital capacity [FVC]), and improved walking ability (e.g., six-minute walk test [6MWT]).(8) Other treatments of MPS VII are symptomatic and supportive. Bone deformities, hernias, ocular abnormalities, and cardiovascular abnormalities may require surgical correction.(36)
Lysosomal Acid Lipase Deficiency (LAL-D)	LAL-D is a progressive and rare lysosomal storage disorder caused by mutations in the *LIPA* gene, causing deficiency of the enzyme lysosomal acid lipase (LAL). This enzyme plays a critical role in the degradation of triglycerides and cholesteryl esters. Deficiency of LAL enzyme subsequently causes cholesterol esters and triglycerides to accumulate in the lysosomes, leading to increased levels of plasma cholesterol.(38,39,40) The phenotypic spectrum ranges from the infantile-onset form referred to as Wolman disease, to a later-onset form known as cholesteryl ester storage disease (CESD).(38,40) Wolman disease usually leads to death before 6 months of age, and is characterized by poor growth, diarrhea, anemia, massive hepatosplenomegaly, and rapidly progressive liver dysfunction. The less-severe CESD presents later in life with such findings as elevated liver function tests, dyslipidemia, hepatosplenomegaly, and/or gastrointestinal symptoms.(38-40) The manifestations of LAL-D, especially CESD, can mimic and be mistaken for other cardiovascular and liver diseases (e.g., familial hypercholesterolemia, non-alcoholic steatohepatitis).(38) Diagnosis is confirmed with genetic testing for biallelic pathogenic variants in the *LIPA* gene, or demonstration of deficient LAL enzyme activity (less than or equal to 11% of mean normal) in leukocytes, fibroblasts, or dried blood spots.(38) Prior to the availability of sebelipase alfa (Kanuma), treatment was limited to controlling cholesterol levels and preventing atherosclerotic events with HMG-CoA reductase inhibitors, and blood transfusions and/or liver transplantation.(38-40) HMG-CoA reductase inhibitors (statins) are often attempted as a way to correct high low-density lipoprotein cholesterol (LDL-C) levels, but therapeutic response is frequently insufficient, requiring high doses of statins, or combinations with other lipid-lowering medications. In addition, statin therapy has not uniformly been shown to have a beneficial effect on hepatic steatosis or serum transaminase concentrations, thus liver disease will progress in LAL-D patients treated only with statins.(40,41) Given the historical morbidity and mortality of LAL-D, treatment with enzyme replacement therapy sebelipase alfa should be initiated as soon as the diagnosis of LAL-D is established. Sebelipase alfa has demonstrated increased growth (weight and height), decreases in ALT, AST, and total bilirubin, decreases in serum triglycerides and LDL-C levels, an increase in high-density lipoprotein cholesterol (HDL-C), and overall prolonged survival.(6,38,39,40,41)
Pompe Disease	Pompe disease, also known as acid maltase deficiency (AMD) or glycogen storage disease type II (GSDII), is an autosomal recessive disorder caused by mutations in the *GAA* gene for enzyme acid alpha-glucosidase (GAA). Deficiency of lysosomal enzyme GAA leads to accumulation of glycogen in lysosomes and cytoplasm, resulting in tissue destruction.(42) Infantile-onset Pompe disease (IOPD) is characterized by cardiomyopathy, severe generalized hypotonia, respiratory distress typically requiring ventilator support, and failure to thrive. Most patients with this form die within the first year or two of life without treatment. The juvenile-adult form (late onset Pompe disease [LOPD]) is

	characterized by skeletal myopathy, delayed gross-motor development, and respiratory insufficiency and/or failure.(42) Diagnosis can be confirmed by demonstration of reduced acid alpha-glucosidase glycogen enzyme activity in dried blood spots or leukocytes (skin fibroblasts or skeletal muscle tissue are also options). *GAA* gene mutational analysis is the preferred test to confirm the diagnosis (with two pathogenic alleles), since it is routinely available, less invasive, and may help predict cross-reactive immunologic material (CRIM) status.(42,44) Prenatal diagnosis is possible by DNA analysis of cultured amniocytes or chorionic villus samples, if the mutation in the family is known.(44) The advent of enzyme replacement therapy (ERT) with alglucosidase alfa (Lumizyme) has improved clinical outcomes and survival for both IOPD and LOPD. For patients with IOPD, clinical studies have demonstrated improvements in survival, decreased need for ventilatory support, and improvements in cardiac and skeletal muscle function. For patients with LOPD, demonstrated improvements have occurred with walking distance, pulmonary function (forced vital capacity [FVC]), and survival.(7,44) Guidelines note that a trial of ERT may be considered in patients who receive invasive ventilation support, if there are predefined outcomes which can be evaluated and which, if achieved, would improve the functional status of the patient. After one year, decisions regarding the continuation of ERT in patients receiving invasive ventilation support should be made on a case-by-case basis.(46,47) Treatment outcomes in IOPD (not LOPD) are affected by cross-reactive immunologic material (CRIM) status. CRIM status, as determined by mutational analysis, determines whether a patient completely lacks endogenous acid alpha-glucosidase glycogen enzyme (CRIM-negative) or has some residual enzyme activity (CRIM-positive). Patients with CRIM-negative status (approximately 20% of IOPD patients) develop high levels of IgG antibodies to exogenous enzyme, thus rendering ERT ineffective. CRIM-negative status was also associated with regression in motor milestones, clinical decline, and eventual invasive ventilation and death. Immunomodulation protocols that prevent or eliminate immune responses may allow CRIM-negative patients to reap the benefits of ERT. This has successfully been achieved, demonstrating encouraging results, with regimens of rituximab, methotrexate, and/or intravenous immunoglobulin (IVIG).(42,44,47) Nexviazyme (avalglucosidase alfa-ngpt) was approved August 2021 for LOPD in patients age 1 or over. Clinical studies have demonstrated improvements in pulmonary function (FVC) and walking distance.(53) Opfolda (miglustat) in combination with Pombiliti (an ERT; cipaglucosidase alfa-atga) was approved by the FDA in September 2023 as a new treatment for adults with LOPD. Pombiliti provides an exogenous source of GAA, which exerts enzymatic activity in cleaving accumulating glycogen. Opfolda binds with, stabilizes, and reduces inactivation of Pombiliti in the blood after infusion. Clinical studies have demonstrated improvements in pulmonary function (FVC) and walking distance.(59)
Safety	Cerezyme, Elelyso, Fabrazyme, Kanuma, Naglazyme, and Vpriv have no boxed warnings nor contraindications.(2,4,5,6,9,11) Aldurazyme has the following boxed warnings:(1) • Hypersensitivity reactions including anaphylaxis: Patients treated with Aldurazyme have experienced hypersensitivity reactions, including anaphylaxis. Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available during Aldurazyme administration. If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, discontinue Aldurazyme immediately and initiate appropriate medical treatment. In patients with severe hypersensitivity reaction, a desensitization procedure to Aldurazyme may be considered.

	• Patients with compromised respiratory function or acute respiratory disease may be at risk of serious acute exacerbation of their respiratory compromise due to infusion reactions and require additional monitoring Elaprase has the following boxed warning:(3) • Life-threatening anaphylactic reactions have occurred in some patients during and up to 24 hours after infusions. Anaphylaxis, presenting as respiratory distress, hypoxia, hypotension, urticaria and/or angioedema of throat or tongue have been reported to occur during and after infusions, regardless of duration of the course of treatment. Closely observe patients during and after administration and be prepared to manage anaphylaxis. Inform patients of the signs and symptoms of anaphylaxis and have them seek immediate medical care should symptoms occur. Patients with compromised respiratory function or acute respiratory disease may be at risk of serious acute exacerbation of their respiratory compromise due to hypersensitivity reactions, and require additional monitoring. Elfabrio has the following boxed warning:(58) • Hypersensitivity reactions, including anaphylaxis have been experienced in some patients. Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available during administration. If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, discontinue immediately and initiate appropriate medical treatment. In patients with severe hypersensitivity reaction, a desensitization procedure may be considered. Lumizyme has the following boxed warnings:(7) • Life-threatening anaphylactic reactions and severe hypersensitivity reactions have occurred in some patients during and after alglucosidase alfa infusions. Immune-mediated reactions presenting as proteinuria, nephrotic syndrome, and necrotizing skin lesions have occurred in some patients following alglucosidase alfa treatment. Closely observe patients during and after alglucosidase alfa administration and be prepared to manage anaphylaxis and hypersensitivity reactions. Inform patients of the signs and symptoms of anaphylaxis, hypersensitivity reactions, and immune-mediated reactions and have them seek immediate medical care should signs and symptoms occur. • Infantile-onset Pompe disease patients with compromised cardiac or respiratory function may be at risk of serious acute exacerbation of their cardiac or respiratory compromise due to fluid overload, and require additional monitoring. Mepsevii has the following boxed warnings:(8) • Anaphylaxis has occurred with Mepsevii administration, as early as the first dose, therefore appropriate medical support should be readily available when administered. • Closely observe patients during and for 60 minutes after infusion. • Immediately discontinue the infusion if the patient experiences anaphylaxis Nexviazyme has the following boxed warnings:(53) • Hypersensitivity reactions including anaphylaxis: Patients treated with Nexviazyme have experienced life-threatening hypersensitivity reactions, including anaphylaxis. Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available during Nexviazyme administration. If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs Nexviazyme should be discontinued immediately and

	appropriate medical treatment should be initiated. In patients with severe hypersensitivity reaction a desensitization procedure may be considered. • Infusion-associated reactions (IARs): Patients treated with Nexviazyme have experienced severe IARs. If severe IARs occur, consider immediate discontinuation of Nexviazyme, initiation of appropriate medical treatment, and the benefits and risks of readministering Nexviazyme. Patients with an acute underlying illness at the time of Nexviazyme infusion may be at greater risk for IARs. Patients with advanced Pompe disease may have compromised cardiac and respiratory function, which may predispose them to a higher risk of severe complications from IARs. • Risk of acute cardiorespiratory failure in susceptible patients: Patients susceptible to fluid volume overload, or those with acute underlying respiratory illness or compromised cardiac or respiratory function for whom fluid restriction is indicated may be at risk of serious exacerbation of their cardiac or respiratory status during Nexviazyme infusion. More frequent monitoring of vitals should be performed during Nexviazyme infusion in such patients. Pombiliti is contraindicated in pregnancy, and has the following boxed warnings:(59) • Hypersensitivity reactions including anaphylaxis: Patients treated with Pombiliti have experienced life-threatening hypersensitivity reactions, including anaphylaxis. Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available during Pombiliti administration. If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs Pombiliti should be discontinued immediately and appropriate medical treatment should be initiated. In patients with severe hypersensitivity reaction, desensitization measures to Pombiliti may be considered. • Infusion-associated reactions (IARs): Patients treated with Pombiliti have experienced severe IARs. If severe IARs occur, immediately discontinue the Pombiliti infusion, initiate appropriate medical treatment, and assess the benefits and risks of readministering Pombiliti following severe IARs. Patients with an acute underlying illness at the time of Pombiliti infusion may be at greater risk for IARs. Patients with advanced Pompe disease may have compromised cardiac and respiratory function, which may predispose them to a higher risk of severe complications from IARs. • Risk of acute cardiorespiratory failure in susceptible patients: Patients susceptible to fluid volume overload, or those with acute underlying respiratory illness or compromised cardiac or respiratory function for whom fluid restriction is indicated may be at risk of serious exacerbation of their cardiac or respiratory status during Pombiliti infusion. More frequent monitoring of vitals should be performed during Pombiliti infusion in such patients. Vimizim has the following boxed warning:(10) • Life-threatening anaphylactic reactions have occurred in some patients during Vimizim infusions. Anaphylaxis, presenting as cough, erythema, throat tightness, urticaria, flushing, cyanosis, hypotension, rash, dyspnea, chest discomfort, and gastrointestinal symptoms in conjunction with urticaria, have been reported to occur during infusions, regardless of duration of the course of treatment. Closely observe patients during and after Vimizim administration and be prepared to manage anaphylaxis. Inform patients of the signs and symptoms of anaphylaxis and have them seek immediate medical care should symptoms occur. Patients with acute respiratory illness may be at risk of serious acute exacerbation of their respiratory compromise due to hypersensitivity reactions, and require additional monitoring. Xenpozyme has the following boxed warning:(54)

	• Hypersensitivity reactions including anaphylaxis: Patients treated with Xenpozyme have experienced hypersensitivity reactions, including anaphylaxis. Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available during Xenpozyme administration. If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs Xenpozyme should be discontinued immediately and appropriate medical treatment should be initiated. In patients with severe hypersensitivity reaction, a desensitization procedure to Xenpozyme may be considered.

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POLICY AGENT SUMMARY – MEDICAL PRIOR AUTHORIZATION

HCPC Codes	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
J1931	Aldurazyme	laronidase soln for iv infusion	2.9 MG/5ML	M ; N ; O ; Y	N		
J1786	Cerezyme	imiglucerase for inj	400 UNIT	M ; N ; O ; Y	N		
J1743	Elaprase	idursulfase soln for iv infusion	6 MG/3ML	M ; N ; O ; Y	N		
J3060	Elelyso	taliglucerase alfa for inj	200 UNIT	M ; N ; O ; Y	N		
J2508	Elfabrio	pegunigalsidase alfa-iwxj iv solution	20 MG/10ML ; 5 MG/2.5ML	M ; N ; O ; Y	N		
J0180	Fabrazyme	agalsidase beta for iv soln	35 MG ; 5 MG	M ; N ; O ; Y	N		
J2840	Kanuma	sebelipase alfa iv soln	20 MG/10ML	M ; N ; O ; Y	N		
J0221	Lumizyme	alglucosidase alfa for iv soln	50 MG	M ; N ; O ; Y	N		
J3397	Mepsevii	vestronidase alfa-vjbk iv soln	10 MG/5ML	M ; N ; O ; Y	N		
J1458	Naglazyme	galsulfase soln for iv infusion	1 MG/ML	M ; N ; O ; Y	N		
J0219	Nexviazyme	avalglucosidase alfa-ngpt for iv soln	100 MG	M ; N ; O ; Y	N		
G0138 ; J1203	Pombiliti	cipaglucosidase alfa-atga for iv soln	105 MG	M ; N ; O ; Y	N		
J1322	Vimizim	elosulfase alfa soln for iv infusion	5 MG/5ML	M ; N ; O ; Y	N		
J3385	Vpriv	velaglucerase alfa for inj	400 UNIT	M ; N ; O ; Y	N		
J0218	Xenpozyme	olipudase alfa-rpcp for iv soln	20 MG ; 4 MG	M ; N ; O ; Y	N		

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Aldurazyme	laronidase soln for iv infusion	2.9 MG/5ML	Commercial ; HIM ; ResultsRx
Cerezyme	imiglucerase for inj	400 UNIT	Commercial ; HIM ; ResultsRx
Elaprase	idursulfase soln for iv infusion	6 MG/3ML	Commercial ; HIM ; ResultsRx
Elelyso	taliglucerase alfa for inj	200 UNIT	Commercial ; HIM ; ResultsRx
Elfabrio	pegunigalsidase alfa-iwxj iv solution	20 MG/10ML ; 5 MG/2.5ML	Commercial ; HIM ; ResultsRx
Fabrazyme	agalsidase beta for iv soln	35 MG ; 5 MG	Commercial ; HIM ; ResultsRx
Kanuma	sebelipase alfa iv soln	20 MG/10ML	Commercial ; HIM ; ResultsRx
Lumizyme	alglucosidase alfa for iv soln	50 MG	Commercial ; HIM ; ResultsRx
Mepsevii	vestronidase alfa-vjbk iv soln	10 MG/5ML	Commercial ; HIM ; ResultsRx
Naglazyme	galsulfase soln for iv infusion	1 MG/ML	Commercial ; HIM ; ResultsRx
Nexviazyme	avalglucosidase alfa-ngpt for iv soln	100 MG	Commercial ; HIM ; ResultsRx
Pombiliti	cipaglucosidase alfa-atga for iv soln	105 MG	Commercial ; HIM ; ResultsRx
Vimizim	elosulfase alfa soln for iv infusion	5 MG/5ML	Commercial ; HIM ; ResultsRx
Vpriv	velaglucerase alfa for inj	400 UNIT	Commercial ; HIM ; ResultsRx
Xenpozyme	olipudase alfa-rpcp for iv soln	20 MG ; 4 MG	Commercial ; HIM ; ResultsRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Aldurazyme	**Mucopolysaccharidosis type I [MPS I] (Hurler, Hurler-Scheie, and Scheie Syndromes)** **Initial Evaluation** **Aldurazyme** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following: **Agents Eligible for Continuation of Therapy** Aldurazyme 1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** 2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR** B. BOTH of the following: 1. The patient has a diagnosis of mucopolysaccharidosis type I (MPS I – Hurler, Hurler-Scheie, or Scheie syndrome) and ONE of the following: A. The patient has alpha-L-iduronidase enzyme activity less than 10% of mean normal in leukocytes, fibroblasts, plasma, serum, or dried blood spots **OR** B. Genetic analysis confirms mutation in the alpha-L-iduronidase (*IDUA*) gene **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 2. The prescriber has assessed current status of the following: joint mobility and range of motion, walking capacity (e.g., six-minute walk test [6MWT]), cardiac function, respiratory function (e.g., forced vital capacity [FVC]), liver and spleen volumes, number of sleep apnea/hypopnea episodes, growth velocity, urinary glycosaminoglycans (GAGs) **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 5. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval**: 12 months **Renewal Evaluation** **Aldurazyme** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Medical Drug Review process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND**

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>2. The patient has had improvements or stabilization with the requested agent as indicated by ONE of the following:
A. Joint mobility and/or range of motion OR
B. Respiratory function (e.g., sleep apnea/hypopnea, forced vital capacity [FVC]) OR
C. Cardiac function (e.g., left ventricular hypertrophy) OR
D. Liver and/or spleen volume OR
E. Urinary glycosaminoglycans (GAGs) OR
F. Growth velocity OR
G. Walking capacity (e.g., six-minute walk test [6MWT]) AND
3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis AND
4. The patient does NOT have any FDA labeled contraindications to the requested agent AND
5. The requested quantity (dose) is within FDA labeled dosing for the requested indication

Length of Approval: 12 months</td></tr>
<tr><td>Cerezyme, Elelyso, and Vpriv</td><td>Gaucher Disease

<table><tr><th>Indication</th><th>Preferred Agents</th><th>Non-Preferred Agents</th></tr><tr><td>Gaucher disease</td><td>Vpriv</td><td>Cerezyme, Elelyso</td></tr></table>
Initial Evaluation

Cerezyme, Elelyso, and Vpriv will be approved when ALL of the following are met:

1. ONE of the following:
A. The requested agent is eligible for continuation of therapy AND BOTH of the following:

<table><tr><th>Agents Eligible for Continuation of Therapy</th></tr><tr><td>All target agents are eligible for continuation of therapy</td></tr></table>
1. ONE of the following:
A. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days OR
B. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed AND
2. The prescriber has assessed current status of the following: hemoglobin level, platelet count, liver and spleen volumes, evidence of bone disease, growth velocity OR
B. The patient has a diagnosis of Gaucher disease type 1 (GD1) and ALL of the following:
1. The patient does NOT have any neuronopathic symptoms indicative of Gaucher disease type 2 or type 3 [e.g., bulbar signs (e.g., stridor, strabismus, swallowing difficulty), pyramidal signs (e.g., opisthotonos, head retroflexion, spasticity, trismus), oculomotor apraxia, tonic-clonic seizures, myoclonic epilepsy, dementia, ataxia] AND</td></tr>
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Module	Clinical Criteria for Approval
	2. Diagnosis has been confirmed by at least ONE of the following: A. The patient has baseline (prior to therapy for the requested indication) glucocerebrosidase enzyme activity of less than or equal to 15% of mean normal in fibroblasts, leukocytes, or other nucleated cells **OR** B. Genetic analysis confirms two (2) pathogenic alleles in the glucocerebrosidase (*GBA*) gene **AND** 3. The patient has at least ONE of the following clinical presentations at baseline (prior to therapy for the requested indication): A. Anemia defined as mean hemoglobin (Hb) level below the testing laboratory's lower limit of the normal range based on age and gender **OR** B. Thrombocytopenia (platelet count less than 100,000/microliter on at least 2 measurements) **OR** C. Hepatomegaly **OR** D. Splenomegaly **OR** E. Growth failure (i.e., growth velocity below the standard mean for age) **OR** F. Evidence of bone disease with other causes ruled out **AND** 4. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 2. If the client has preferred agent(s), then ONE of the following: A. The requested agent is a preferred agent **OR** B. The patient is at least 2 years of age and less than 4 years of age **OR** C. The patient has tried and had an inadequate response, has an intolerance, or has a hypersensitivity to ONE preferred agent **OR** D. The patient has an FDA labeled contraindication to ALL preferred agent(s) **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient will NOT be using the requested agent in combination with another enzyme replacement therapy for the requested indication **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 6. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval**: 12 months **Renewal Evaluation** **Cerezyme, Elelyso, and Vpriv** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Medical Drug Review process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had improvements or stabilization with the requested agent as indicated by ONE of the following: A. Hemoglobin level **OR** B. Platelet count (sufficient to decrease the risk of bleeding) **OR** C. Liver volume **OR** D. Spleen volume **OR** E. Growth velocity **OR** F. Bone pain or disease **AND** 3. If the client has preferred agent(s), then ONE of the following: A. The requested agent is a preferred agent for the requested indication **OR** B. The patient is at least 2 years of age and less than 4 years of age **OR**

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
C. The patient has tried and had an inadequate response, has an intolerance, or has a hypersensitivity to ONE preferred agent OR
D. The patient has an FDA labeled contraindication to ALL preferred agent(s) AND
4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis AND
5. The patient will NOT be using the requested agent in combination with another enzyme replacement therapy for the requested indication AND
6. The patient does NOT have any FDA labeled contraindications to the requested agent AND
7. The requested quantity (dose) is within FDA labeled dosing for the requested indication

Length of Approval: 12 months
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<tr><td>Elaprase</td><td>
Mucopolysaccharidosis type II [MPS II] (Hunter Syndrome)

Initial Evaluation

Elaprase will be approved when ALL of the following are met:

1. ONE of the following:
A. The requested agent is eligible for continuation of therapy AND ONE of the following:

<table>
<tr><th>Agents Eligible for Continuation of Therapy</th></tr>
<tr><td>Elaprase</td></tr>
</table>

1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days OR
2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed OR
B. BOTH of the following:
1. The patient has a diagnosis of mucopolysaccharidosis type II (MPS II – Hunter syndrome) confirmed by at least ONE of the following:
A. The patient has iduronate-2-sulfatase enzyme deficiency in leukocytes, fibroblasts, plasma, or dried blood spots in the presence of normal activity of at least one other sulfatase enzyme OR
B. Genetic analysis confirms mutation in the iduronate-2-sulfatase (IDS) gene AND
2. If the patient has an FDA labeled indication, then ONE of the following:
A. The patient's age is within FDA labeling for the requested indication for the requested agent OR
B. There is support for using the requested agent for the patient's age for the requested indication AND
2. The prescriber has assessed current status of the following: musculoskeletal function (e.g., joint stiffness, pelvic dysplasia, vertebral and rib abnormalities, dysostosis multiplex), cardiac function, respiratory dysfunction (e.g., sleep apnea/hypopnea, recurrent infection, forced vital capacity [FVC]), walking capacity (e.g., six-minute walk test [6MWT]), liver and spleen volumes, urinary glycosaminoglycans (GAGs), growth velocity AND
3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis AND
4. The patient does NOT have any FDA labeled contraindications to the requested agent AND
5. The requested quantity (dose) is within FDA labeled dosing for the requested indication
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<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>Length of Approval: 12 months

Renewal Evaluation

Elaprase will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the plan’s Medical Drug Review process [Note: patients not previously approved for the requested agent will require initial evaluation review] AND
2. The patient has had improvements or stabilization with the requested agent as indicated by ONE of the following:
A. Joint mobility and/or range of motion OR
B. Respiratory function (e.g., sleep apnea/hypopnea, forced vital capacity [FVC]) OR
C. Cardiac function OR
D. Liver and/or spleen volume OR
E. Urinary glycosaminoglycans (GAGs) OR
F. Growth velocity OR
G. Walking capacity (e.g., six-minute walk test [6MWT]) AND
3. The prescriber is a specialist in the area of the patient’s diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient’s diagnosis AND
4. The patient does NOT have any FDA labeled contraindications to the requested agent AND
5. The requested quantity (dose) is within FDA labeled dosing for the requested indication

Length of Approval: 12 months</td></tr>
<tr><td>Elfabrio, Fabrazyme</td><td>Fabry Disease

Initial Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
A. The requested agent is eligible for continuation of therapy AND ONE of the following:

<table><tr><th>Agents Eligible for Continuation of Therapy</th></tr><tr><td>Elfabrio, Fabrazyme</td></tr></table>
1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days OR
2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed OR
B. BOTH of the following:
1. The patient has a diagnosis of Fabry disease confirmed by at least ONE of the following:
A. The patient is male and has a deficiency of alpha-galactosidase A (alpha-Gal A) enzyme activity in leukocytes, fibroblasts, plasma, or dried blood spots OR
B. Genetic analysis confirms a mutation in the galactosidase alpha (GLA) gene AND
2. If the patient has an FDA labeled indication, then ONE of the following:
A. The patient’s age is within FDA labeling for the requested indication for the requested agent OR</td></tr>
</table>

Module	Clinical Criteria for Approval
	B. There is support for using the requested agent for the patient's age for the requested indication **AND** 2. The prescriber has assessed current status of the following: renal function (e.g., proteinuria, glomerular filtration rate [GFR]), cardiac function (e.g., left ventricular hypertrophy, conduction defects, mitral and/or aortic valve abnormalities), ophthalmological signs (e.g., corneal verticillate, subcapsular cataracts, conjunctival and/or retinal vasculopathy), peripheral nerve symptoms (e.g., neuropathic pain, heat and/or cold intolerance, impaired sweat function), and gastrointestinal involvement (e.g., nausea, vomiting, abdominal pain, diarrhea, constipation) **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient will NOT be using the requested agent in combination with another Fabry disease agent (e.g., Elfabrio, Fabrazyme, Galafold) **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 6. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval**: 12 months **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Medical Drug Review process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had improvements or stabilization with the requested agent as indicated by ONE of the following: A. Renal function (e.g., proteinuria, glomerular filtration rate [GFR]) **OR** B. Cardiac function (e.g., left ventricular hypertrophy, conduction defects, mitral and/or aortic valve abnormalities) **OR** C. Ophthalmological signs (e.g., corneal verticillate, subcapsular cataracts, conjunctival and/or retinal vasculopathy) **OR** D. Peripheral nerve symptoms (e.g., neuropathic pain, heat and/or cold intolerance, impaired sweat function) **OR** E. Gastrointestinal symptoms (e.g., nausea, vomiting, abdominal pain, diarrhea, constipation) **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient will NOT be using the requested agent in combination with another Fabry disease agent (e.g., Elfabrio, Fabrazyme, Galafold) **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 6. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval**: 12 months
Kanuma	**Lysosomal Acid Lipase Deficiency (LAL-D)** **Initial Evaluation** **Kanuma** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following:

Module	Clinical Criteria for Approval
	Agents Eligible for Continuation of Therapy Kanuma 1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** 2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR** B. BOTH of the following: 1. The patient has a diagnosis of lysosomal acid lipase deficiency (LAL-D) confirmed by at least ONE of the following: A. The patient has lysosomal acid lipase (LAL) enzyme activity less than or equal to 11% of mean normal in leukocytes, fibroblasts, or dried blood spots **OR** B. Genetic analysis confirms biallelic mutation (two pathogenic variants) in the *LIPA* gene **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 2. The prescriber has assessed current status of the following: growth velocity, serum transaminases (e.g., ALT, AST), bilirubin, lipid levels (e.g., LDL-C, TG, HDL-C), and liver volume **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 5. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval:** 12 months **Renewal Evaluation** **Kanuma** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Medical Drug Review process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had improvements or stabilization with the requested agent as indicated by ONE of the following: A. Growth (e.g., height and/or weight) **OR** B. Lipid levels (e.g., LDL-C, TG, HDL-C) **OR** C. Serum transaminases (e.g., ALT, AST) and/or bilirubin **OR** D. Liver volume **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 5. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval:** 12 months
Lumizyme	**Pompe Disease**

Module	Clinical Criteria for Approval
	Initial Evaluation **Lumizyme** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following: **Agents Eligible for Continuation of Therapy** Lumizyme 1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** 2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR** B. The patient has a diagnosis of Pompe disease (acid maltase deficiency [AMD]; glycogen storage disease type II [GSDII]) confirmed by at least ONE of the following: 1. Genetic analysis confirms biallelic mutation (two pathogenic variants) in the *GAA* gene **OR** 2. The patient has deficient acid alpha-glucosidase glycogen enzyme activity in dried blood spots, leukocytes, skin fibroblasts, and/or skeletal muscle tissue **AND** 2. The prescriber has assessed current status of the following: gross motor function (e.g., walking distance, skeletal muscle function, hypotonia)**,** pulmonary function (e.g., forced vital capacity [FVC], need for ventilatory support), cardiac function (e.g., cardiomyopathy) **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 5. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval**: 12 months **Renewal Evaluation** **Lumizyme** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Medical Drug Review process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had improvements or stabilization with the requested agent as indicated by ONE of the following: A. Gross motor function (e.g., walking distance, skeletal muscle function, hypotonia) **OR** B. Pulmonary function (e.g., forced vital capacity [FVC], need for ventilatory support) **OR** C. Cardiac function (e.g., cardiomyopathy) **AND** 3. ONE of the following: A. There is no evidence that the patient has developed IgG antibodies to the requested agent **OR** B. The patient developed IgG antibodies to the requested agent, but is following immunomodulation protocol (e.g., methotrexate, rituximab, intravenous immunoglobulin) to prevent or eliminate immune responses **AND**

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<tr><td></td><td>4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis AND
5. The patient does NOT have any FDA labeled contraindications to the requested agent AND
6. The requested quantity (dose) is within FDA labeled dosing for the requested indication

Length of Approval: 12 months</td></tr>
<tr><td>Mepsevii</td><td>Mucopolysaccharidosis type VII [MPS VII] (Sly Syndrome)

Initial Evaluation

Mepsevii will be approved when ALL of the following are met:

1. ONE of the following:
A. The requested agent is eligible for continuation of therapy AND ONE of the following:

<table><tr><th>Agents Eligible for Continuation of Therapy</th></tr><tr><td>Mepsevii</td></tr></table>
1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days OR
2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed OR
B. The patient has a diagnosis of mucopolysaccharidosis type VII (MPS VII – Sly syndrome) confirmed by at least ONE of the following:
1. The patient has a beta-glucuronidase enzyme deficiency in cultured leukocytes or fibroblasts OR
2. Genetic analysis confirms mutation in the beta-glucuronidase (GUSB) gene AND
2. The prescriber has assessed current status of the following: skeletal manifestations (e.g., joint mobility, dysostosis multiplex), walking capacity (e.g. six-minute walk test [6MWT]), respiratory function (e.g., forced vital capacity [FVC]), liver and spleen volumes AND
3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis AND
4. The patient does NOT have any FDA labeled contraindications to the requested agent AND
5. The requested quantity (dose) is within FDA labeled dosing for the requested indication

Length of Approval: 12 months

Renewal Evaluation

Mepsevii will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the plan's Medical Drug Review process [Note: patients not previously approved for the requested agent will require initial evaluation review] AND
2. The patient has had improvements or stabilization with the requested agent as indicated by ONE of the following:
A. Walking capacity (e.g., six-minute walk test [6MWT]) OR
B. Respiratory function (e.g., forced vital capacity [FVC]) OR
C. Liver and/or spleen volume AND</td></tr>
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Module	Clinical Criteria for Approval
	3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 5. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval**: 12 months
Naglazyme	**Mucopolysaccharidosis type VI [MPS VI] (Maroteaux-Lamy Syndrome)** **Initial Evaluation** **Naglazyme** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following: **Agents Eligible for Continuation of Therapy** Naglazyme 1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** 2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR** B. The patient has a diagnosis of mucopolysaccharidosis type VI (MPS VI – Maroteaux-Lamy syndrome) confirmed by at least ONE of the following: 1. The patient has arylsulfatase B enzyme activity less than 10% of the lower limit of normal in cultured fibroblasts or isolated leukocytes, and has normal enzyme activity in at least one other sulfatase enzyme **OR** 2. Genetic analysis confirms mutation in the arylsulfatase B (*ARSB*) gene **AND** 2. The prescriber has assessed current status of the following: skeletal manifestations (e.g., joint mobility, bone disease), walking capacity (e.g., six-minute walk test [6MWT]), cardiac function, respiratory function (e.g., forced vital capacity [FVC]), liver and spleen volumes, growth velocity, urinary glycosaminoglycans (GAGs) **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 5. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval**: 12 months **Renewal Evaluation** **Naglazyme** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Medical Drug Review process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had improvements or stabilization with the requested agent as indicated by ONE of the following: A. Joint mobility and/or range of motion **OR**

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B. Walking capacity (e.g. six-minute walk test [6MWT]) OR
C. Cardiac function OR
D. Urinary glycosaminoglycans (GAGs) OR
E. Respiratory function (e.g., forced vital capacity [FVC]) OR
F. Liver and/or spleen volume OR
G. Growth velocity AND
3. The prescriber is a specialist in the area of the patient’s diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient’s diagnosis AND
4. The patient does NOT have any FDA labeled contraindications to the requested agent AND
5. The requested quantity (dose) is within FDA labeled dosing for the requested indication

Length of Approval: 12 months
</td></tr>
<tr><td>Nexviazyme</td><td>
Pompe Disease

Initial Evaluation

Nexviazyme will be approved when ALL of the following are met:

1. ONE of the following:
A. The requested agent is eligible for continuation of therapy AND ONE of the following:

<table>
<tr><th>Agents Eligible for Continuation of Therapy</th></tr>
<tr><td>Nexviazyme</td></tr>
</table>

1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days OR
2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed OR
B. The patient has a diagnosis of late-onset Pompe disease (acid maltase deficiency [AMD]; glycogen storage disease type II [GSDII]) confirmed by at least ONE of the following:
1. Genetic analysis confirms biallelic mutation (two pathogenic variants) in the GAA gene OR
2. The patient has deficient acid alpha-glucosidase glycogen enzyme activity in dried blood spots, leukocytes, skin fibroblasts, and/or skeletal muscle tissue AND
2. The prescriber has assessed current status of the following: gross motor function (e.g., walking distance), pulmonary function (e.g., forced vital capacity [FVC]) AND
3. The prescriber is a specialist in the area of the patient’s diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient’s diagnosis AND
4. The patient does NOT have any FDA labeled contraindications to the requested agent AND
5. The requested quantity (dose) is within FDA labeled dosing for the requested indication

Length of Approval: 12 months

Renewal Evaluation

Nexviazyme will be approved when ALL of the following are met:
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<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>1. The patient has been previously approved for the requested agent through the plan's Medical Drug Review process [Note: patients not previously approved for the requested agent will require initial evaluation review] AND
2. The patient has had improvements or stabilization with the requested agent as indicated by ONE of the following:
A. Gross motor function (e.g., walking distance) OR
B. Pulmonary function (e.g., forced vital capacity [FVC]) AND
3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis AND
4. The patient does NOT have any FDA labeled contraindications to the requested agent AND
5. The requested quantity (dose) is within FDA labeled dosing for the requested indication

Length of Approval: 12 months</td></tr>
<tr><td>Pombiliti</td><td>Pompe Disease

Initial Evaluation

Pombiliti will be approved when ALL of the following are met:

1. ONE of the following:
A. The requested agent is eligible for continuation of therapy AND ONE of the following:

<table><tr><th>Agents Eligible for Continuation of Therapy</th></tr><tr><td>Pombiliti</td></tr></table>
1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days OR
2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed OR
B. ALL of the following:
1. The patient has a diagnosis of late-onset Pompe disease (acid maltase deficiency [AMD]; glycogen storage disease type II [GSDII]) confirmed by at least ONE of the following:
A. Genetic analysis confirms biallelic mutation (two pathogenic variants) in the GAA gene OR
B. The patient has deficient acid alpha-glucosidase glycogen enzyme activity in dried blood spots, leukocytes, skin fibroblasts, and/or skeletal muscle tissue AND
2. The patient is not improving on their current enzyme replacement therapy (ERT) AND
3. The requested agent will be taken in combination with Opfolda AND
4. If the patient has an FDA labeled indication, then ONE of the following:
A. The patient's age is within FDA labeling for the requested indication for the requested agent OR
B. There is support for using the requested agent for the patient's age for the requested indication AND
2. The prescriber has assessed current status of the following: gross motor function (e.g., walking distance), pulmonary function (e.g., forced vital capacity [FVC]) AND
3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis AND
4. The patient does NOT have any FDA labeled contraindications to the requested agent AND
5. The requested quantity (dose) is within FDA labeled dosing for the requested indication</td></tr>
</table>

Module	Clinical Criteria for Approval
	Length of Approval: 12 months **Renewal Evaluation** **Pombiliti** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Medical Drug Review process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had improvements or stabilization with the requested agent as indicated by ONE of the following: A. Gross motor function (e.g., walking distance) **OR** B. Pulmonary function (e.g., forced vital capacity [FVC]) **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 5. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval**: 12 months
Vimizim	**Mucopolysaccharidosis type IVA [MPS IVA] (Morquio A Syndrome)** **Initial Evaluation** **Vimizim** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following: **Agents Eligible for Continuation of Therapy** Vimizim 1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** 2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR** B. BOTH of the following: 1. The patient has a diagnosis of mucopolysaccharidosis type IVA (MPS IVA – Morquio A syndrome) confirmed by at least ONE of the following: A. The patient has a *N*-acetylgalactosamine-6-sulfatase deficiency in leukocytes or fibroblasts **OR** B. Genetic analysis confirms mutation in the galactosamine (N-acetyl)-6-sulfatase (*GALNS*) gene **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 2. The prescriber has assessed current status of the following: walking capacity (e.g., six-minute walk test [6MWT]) and forced vital capacity (FVC) **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND**

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>4. The patient does NOT have any FDA labeled contraindications to the requested agent AND
5. The requested quantity (dose) is within FDA labeled dosing for the requested indication

Length of Approval: 12 months

Renewal Evaluation

Vimizim will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the plan’s Medical Drug Review process [Note: patients not previously approved for the requested agent will require initial evaluation review] AND
2. The patient has had improvements or stabilization with the requested agent as indicated by ONE of the following:
A. Walking capacity (e.g., six-minute walk test [6MWT]) OR
B. Forced vital capacity (FVC) AND
3. The prescriber is a specialist in the area the patient’s diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient’s diagnosis AND
4. The patient does NOT have any FDA labeled contraindications to the requested agent AND
5. The requested quantity (dose) is within FDA labeled dosing for the requested indication

Length of Approval: 12 months</td></tr>
<tr><td>Xenpozyme</td><td>Acid Sphingomyelinase Deficiency (ASMD) (Niemann-Pick Disease Type A, A/B, B)

Initial Evaluation

Xenpozyme will be approved when ALL of the following are met:

1. ONE of the following:
A. The requested agent is eligible for continuation of therapy AND BOTH of the following:

<table><tr><th>Agents Eligible for Continuation of Therapy</th></tr><tr><td>Xenpozyme</td></tr></table>
1. ONE of the following:
A. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days OR
B. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed AND
2. The prescriber has assessed current status of the following: respiratory function (e.g., diffusion capacity of the lungs for carbon monoxide [DLCO]), liver and spleen volumes OR
B. BOTH of the following:
1. The patient has a diagnosis of acid sphingomyelinase deficiency (ASMD) (Niemann-Pick disease types A, A/B, B) and BOTH of the following:
A. ONE of the following:
1. The patient has acid sphingomyelinase enzyme activity less than 10% of mean normal in peripheral leukocytes, cultured fibroblasts, or lymphocytes OR
2. Genetic analysis confirms mutation in the sphingomyelin phosphodiesterase-1 (SMPD1) gene AND</td></tr>
</table>

Module	Clinical Criteria for Approval
	B. The patient has at least ONE of the following clinical presentations at baseline (prior to therapy for the requested indication): 1. Hepatomegaly and/or splenomegaly **OR** 2. Retinal abnormalities (e.g., cherry-red spot of the macula) **OR** 3. Respiratory dysfunction (e.g., interstitial lung disease, decreased diffusion capacity of the lungs for carbon monoxide [DLCO]) **OR** 4. Lipid abnormalities **OR** 5. Osteopenia **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 2. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 4. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval**: 12 months **Renewal Evaluation** **Xenpozyme** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Medical Drug Review process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had improvements or stabilization with the requested agent as indicated by ONE of the following: A. Respiratory function (e.g., diffusion capacity for carbon monoxide [DLCO]) **OR** B. Liver and/or spleen volumes **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 5. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval**: 12 months

