Medical Therapies for Enzyme Deficiencies

Policy Number: CS2022D0052W
Effective Date: December 1, 2022

Instructions for Use

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Related Community Plan Policy
• Intravenous Enzyme Replacement Therapy (ERT) for Gaucher Disease

Application

This Medical Benefit Drug Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Indiana	Medical Therapies for Enzyme Deficiencies (for Indiana Only)
Kansas	Refer to the state's Medicaid clinical policy
Louisiana	Medical Therapies for Enzyme Deficiencies (for Louisiana Only)
North Carolina	None
Texas	Refer to the state's Medicaid clinical policy. Use drug specific criteria found within the *Texas Medicaid Provider Procedures Manual* if available for the specific product; otherwise this Medical Benefit Drug Policy applies.

For the state of Florida, this Medical Benefit Drug Policy only applies to the following enzyme deficiency products; for all other products, refer to the state's Medicaid clinical policy:

HCPCS Code	Drug Product
J0180	Fabrazyme® (agalsidase beta)
J1458	Naglazyme® (galsulfase)
J3490, J3590, C9399	Nulibry™ (fosdenopterin)

Coverage Rationale

This policy refers to the following medical therapies for enzyme deficiency products:

- Aldurazyme® (laronidase)
- Elaprase® (idursulfase)
- Fabrazyme® (agalsidase beta)
- Kanuma® (sebelipase alfa)

- Lumizyme® (alglucosidase alfa)
- Mepsevii™ (vestronidase alfa-vjbk)
- Naglazyme® (galsulfase)
- Nexviazyme™ (avalglucosidase alfa-ngpt)
- Nulibry™ (fosdenopterin)
- Revcovi™ (elapegademase-lvlr)
- Vimizim® (elosulfase alfa)
- Xenpozyme™ (olipudase alfa-rpcp)

Aldurazyme (laronidase) is medically necessary for the treatment of Mucopolysaccharidosis I (MPS I) when the following criteria are met:

- For initial therapy, all of the following:
  - Diagnosis of any of the MPS I syndromes confirmed by one the following:
    - Hurler variant (severe mucopolysaccharidosis I; also, MPS IH)
    - Hurler-Scheie variant (attenuated mucopolysaccharidosis I; also, MPS IHS)
    - Scheie variant (attenuated mucopolysaccharidosis I; also, MPS IS);

    and
  - Diagnosis of MPS I is confirmed by either of the following:
    - Deficiency or absence of fibroblast or leukocyte enzyme activity of alpha-L - iduronidase enzyme activity
    - Molecular genetic confirmation of mutations in the alpha-L-iduronidase gene;

    and
  - Presence of clinical signs and symptoms of the disease (e.g., asymptomatic with affected older sibling, cardiac abnormalities, corneal clouding, dysostosis multiplex, hepatomegaly, restrictive lung disease, etc.); and
  - Dosing is in accordance with the U.S. Food and Drug Administration (FDA) approved labeling; and
  - Initial authorization will be for no more than 12 months
- For continuation of therapy, all of the following:
  - Patient has previously received treatment with laronidase therapy; and
  - Patient has experienced a positive clinical response to laronidase therapy (e.g., improved endurance, improved functional capacity, reduced urine dermatan sulfate/heparan sulfate excretion, etc.); and
  - Dosing is in accordance with the U.S. Food and Drug Administration (FDA) approved labeling; and
  - Reauthorization will be for no more than 12 months

Elaprase (idursulfase) is medically necessary for the treatment of Mucopolysaccharidosis II (MPS II, Hunter Syndrome) when the following criteria are met:

- For initial therapy, all of the following:
  - Diagnosis of MPS II confirmed by one the following:
    - Deficiency in iduronate 2-sulfatase enzyme activity as measured in fibroblasts or leukocytes combined with normal enzyme activity level of another sulfatase
    - Molecular genetic testing for deletion or mutations in the iduronate 2-sulfatase gene;

    and
  - Presence of clinical signs and symptoms of the disease (e.g., hepatosplenomegaly, skeletal deformities, dysostosis, neurocognitive decline, cardiovascular disorders, etc.); and
  - Dosing is in accordance with the U.S. Food and Drug Administration (FDA) approved labeling; and
  - Initial authorization will be for no more than 12 months
- For continuation of therapy, all of the following:
  - Patient has previously received treatment with idursulfase therapy; and
  - Patient has experienced a positive clinical response to idursulfase therapy (e.g., improved endurance, improved functional capacity, reduced spleen volume, reduced urine GAG excretion, etc.); and
  - Dosing is in accordance with the U.S. Food and Drug Administration (FDA) approved labeling; and
  - Reauthorization will be for no more than 12 months

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

- For initial therapy, all of the following:
  - Diagnosis of Fabry disease as confirmed by one the following:

        - Absence or deficiency (< 5% of mean) of normal alpha-galactosidase A (α-Gal A) enzyme activity in leukocytes, dried blood spots, or serum analysis
        - Molecular genetic testing for deletion or mutations in the galactosidase alpha gene;

      and
    - Presence of clinical signs and symptoms of the disease (e.g., Acroparesthesias, angiokeratomas, whorls, anhidrosis/hypo hidrosis, renal disease, exercise/heat/cold intolerance, etc.); and
    - Dosing is in accordance with the U.S. Food and Drug Administration (FDA) approved labeling; and
    - Initial authorization will be for no more than 12 months
- For continuation of therapy, all of the following:
    - Patient has previously received treatment with agalsidase therapy; and
    - Patient has experienced a positive clinical response to agalsidase therapy (e.g., improved renal function, reduction in mean plasma GL-3 levels, decreased GL-3 inclusions, etc.); and
    - Dosing is in accordance with the U.S. Food and Drug Administration (FDA) approved labeling; and
    - Reauthorization will be for no more than 12 months

Kanuma (sebelipase alfa) is medically necessary for the treatment of Lysosomal acid lipase deficiency [LAL - D, Wolman disease (WD), cholesteryl ester disease (CESD)] when the following criteria are met:

- For initial therapy, all of the following:
    - Diagnosis of lysosomal acid lipase deficiency [LAL - D, Wolman disease (WD), cholesteryl ester disease (CESD)] as confirmed by one the following:
        - Absence or deficiency lysosomal acid lipase activity by dried blood spot test
        - Molecular genetic testing for deletion or mutations in the lipase A, lysosomal acid type (LIPA) gene;

      and
    - Presence of clinical signs and symptoms of the disease (e.g., abdominal distention, hepatosplenomegaly, liver fibrosis, ascites, etc.); and
    - Dosing is in accordance with the U.S. Food and Drug Administration (FDA) approved labeling; and
    - Initial authorization will be for no more than 12 months
- For continuation of therapy, all of the following:
    - Patient has previously received treatment with sebelipase therapy; and
    - Patient has experienced a positive clinical response to sebelipase therapy [e.g., improved disease symptoms, improvement of laboratory values (LFTs, cholesterol, triglycerides), etc.]; and
    - Dosing is in accordance with the U.S. Food and Drug Administration (FDA) approved labeling; and
    - Reauthorization will be for no more than 12 months

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

- For initial therapy, one of the following:
    - All of the following for infantile-onset Pompe disease:
        - Diagnosis of infantile-onset Pompe disease as confirmed by one the following:
            - Absence or deficiency (< 1% of the lab specific normal mean) acid alpha-glucosidase deficiency (GAA) activity in skin fibroblasts
            - Molecular genetic testing for deletion or mutations in the GAA gene;

          and
        - Presence of clinical signs and symptoms of the disease (e.g., cardiac hypertrophy, respiratory distress, skeletal muscle weakness, etc.); and
        - Dosing is in accordance with the U.S. Food and Drug Administration (FDA) approved labeling; and
        - Initial authorization will be for no more than 12 months;

      or
    - All of the following for late-onset (non-infantile) Pompe disease:
        - Diagnosis of late-onset Pompe disease as confirmed by one the following:
            - Absence or deficiency (< 40% of the lab specific normal mean) acid alpha-glucosidase deficiency (GAA) activity in lymphocytes, fibroblasts or muscle
            - Molecular genetic testing for deletion or mutations in the GAA gene;

          and

        - Presence of clinical signs and symptoms of the disease (e.g., cardiac hypertrophy, respiratory distress, skeletal muscle weakness, etc.); and
        - Dosing is in accordance with the U.S. Food and Drug Administration (FDA) approved labeling; and
        - Initial authorization will be for no more than 12 months
- For continuation of therapy, all of the following:
    - Patient has previously received treatment with alglucosidase therapy; and
    - Patient has experienced a positive clinical response to alglucosidase therapy (e.g., improved respiratory/cardiac function, improved endurance, etc.); and
    - Dosing is in accordance with the U.S. Food and Drug Administration (FDA) approved labeling; and
    - Reauthorization will be for no more than 12 months

Mepsevii (vestronidase alfa-vjbk) is proven and medically necessary for the treatment of Mucopolysaccharidosis VII (MPS VII, Sly syndrome) when the following criteria are met:
- For initial therapy, all of the following:
    - Diagnosis of Mucopolysaccharidosis VII confirmed by either of the following:
        - Absence or deficiency of fibroblast or leukocyte enzyme activity of beta glucuronidase
        - Molecular genetic confirmation of mutations in the GUSB gene;

      and
    - Presence of clinical signs and symptoms of the disease (e.g., enlarged liver and spleen, joint limitations, airway obstruction or pulmonary problems, limitation of mobility while still ambulatory, etc.); and
    - Dosing is in accordance with the U.S. Food and Drug Administration (FDA) approved labeling; and
    - Initial authorization will be for no more than 12 months
- For continuation of therapy, all of the following:
    - Patient has previously received treatment with vestronidase therapy; and
    - Patient has experienced a positive clinical response to vestronidase therapy (e.g., improved endurance, improved functional capacity, improved pulmonary function, etc.); and
    - Dosing is in accordance with the U.S. Food and Drug Administration (FDA) approved labeling; and
    - Reauthorization will be for no more than 12 months

Naglazyme (galsulfase) is medically necessary for the treatment of Mucopolysaccharidosis VI (MPS VI, Maroteaux-Lamy syndrome) when the following criteria are met:
- For initial therapy, all of the following:
    - Diagnosis of Mucopolysaccharidosis VI confirmed by either of the following:
        - Absence or deficiency of fibroblast or leukocyte enzyme activity of N-acetylgalactosamine 4-sulfatase (arylsulfatase); or
        - Molecular genetic confirmation of mutations in the ASB gene (5q13 - q14)

      and
    - Presence of clinical signs and symptoms of the disease (e.g., kyphoscoliosis, genu valgum, pectus carinatum, gait disturbance, growth deficiency, etc.); and
    - Dosing is in accordance with the U.S. Food and Drug Administration (FDA) approved labeling; and
    - Initial authorization will be for no more than 12 months
- For continuation of therapy, all of the following:
    - Patient has previously received treatment with galsulfase therapy; and
    - Patient has experienced a positive clinical response to galsulfase therapy (e.g., improved endurance, improved functional capacity, reduced urine dermatan sulfate excretion, etc.); and
    - Dosing is in accordance with the U.S. Food and Drug Administration (FDA) approved labeling; and
    - Reauthorization will be for no more than 12 months

Nexviazyme (avalglucosidase alfa-ngpt) proven for the treatment of late-onset Pompe disease. Nexviazyme is medically necessary when the following additional criteria are met:
- For initial therapy, all of the following:
    - Diagnosis of late-onset Pompe disease as confirmed by one the following:
        - Absence or deficiency (< 40% of the lab specific normal mean) acid alpha-glucosidase deficiency (GAA) activity in lymphocytes, fibroblasts or muscle; or
        - Molecular genetic testing for deletion or mutations in the GAA gene

and
    - Presence of clinical signs and symptoms of the disease (e.g., cardiac hypertrophy, respiratory distress, skeletal muscle weakness, etc.); and
    - Dosing is in accordance with the U.S. Food and Drug Administration (FDA) approved labeling; and
    - Initial authorization will be for no more than 12 months
- For continuation of therapy, all of the following:
    - Patient has previously received treatment with avalglucosidase therapy; and
    - Patient has experienced a positive clinical response to avalglucosidase therapy (e.g., improved respiratory/cardiac function, improved endurance, etc.); and
    - Dosing is in accordance with the U.S. Food and Drug Administration (FDA) approved labeling; and
    - Reauthorization will be for no more than 12 months

Nulibry (fosdenopterin) is medically necessary for the treatment of molybdenum cofactor deficiency (MoCD) Type A when the following criteria are met:
- For initial therapy, all of the following:
    - Diagnosis of molybdenum cofactor deficiency (MoCD) Type A confirmed by one of the following:
        - Documentation of confirmed *MOCS1* gene mutation; or
        - Documentation of onset of clinical and/or laboratory signs and symptoms consistent with MoCD Type A (e.g., seizures, exaggerated startle response, high-pitched cry, axial hypotonia, limb hypertonia, feeding difficulties, elevated urinary sulfite and/or S - sulphocysteine (SSC), elevated xanthine in urine or blood, or low or absent uric acid in the urine or blood) within the first 28 days after birth; and
    - Dosing is in accordance with the U.S. Food and Drug Administration (FDA)n approved labeling; and
    - Initial authorization will be for no more than 6 months
- For continuation of therapy, all of the following:
    - Patient has previously received treatment with fosdenopterin therapy; and
    - Confirmation of *MOCS1* gene mutation; and
    - Patient has experienced a positive clinical response to fosdenopterin therapy (e.g., decrease in seizure activity, improvement in feeding/alertness/responsiveness, improvement in gross motor function and/or growth, decreased urinary sulfite or SSC, deceased xanthine in urine or blood, increased uric acid in urine or blood); and
    - Dosing is in accordance with the U.S. Food and Drug Administration (FDA) approved labeling; and
    - Reauthorization will be for no more than 12 months

Revcovi (elapegademase - lvlr) is medically necessary for the treatment of adenosine deaminase severe combined immune deficiency (ADA - SCID) when the following criteria are met:
- For initial therapy, all of the following:
    - Diagnosis of ADA - SCID; and
    - Deficiency of adenosine deaminase is confirmed by any of the following:
        - Deficiency or absence of ADA in plasma, lysed erythrocytes, fibroblasts (cultured from amniotic fluid), or chorionic villus
        - Increase in deoxyadenosine triphosphate (dATP) levels in erythrocyte lysates compared to laboratory standard
        - Decrease in ATP concentration in erythrocytes
        - Molecular genetic confirmation of mutations in both alleles of the ADA1 gene
        - Positive screening by T cell receptor excision circles (TRECs);

      and
    - One of the following:
        - Patient is not a suitable candidate for hematopoietic cell transplantation (HCT)
        - Patient has failed HCT
        - Patient is awaiting HCT;

      and
    - Dosing is in accordance with the U.S. Food and Drug Administration (FDA) approved labeling; and
    - Initial authorization will be for no more than 12 months
- For continuation of therapy, all of the following:
    - Patient has previously received treatment with elapegademase therapy; and
    - Patient has experienced a positive clinical response to elapegademase therapy (e.g., normalization of plasma ADA activity, erythrocyte dATP levels, improvement of disease symptoms, etc.); and

- Dosing is in accordance with the U.S. Food and Drug Administration (FDA) approved labeling; and
- Reauthorization will be for no more than 12 months

Vimizim (elosulfase alfa) is medically necessary for the treatment of Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome) when the following criteria are met:[1,2]

- For initial therapy, all of the following:
  - Diagnosis of Morquio A syndrome confirmed by either of the following:
    - Absence or deficiency of fibroblast or leukocyte GALNS enzyme activity
    - Molecular genetic testing for mutations in the *GALNS* gene (16q24.3);

    and
  - Presence of clinical signs and symptoms of the disease (e.g., kyphoscoliosis, genu valgum, pectus carinatum, gait disturbance, growth deficiency, etc.); and
  - Dosing is in accordance with the U.S. Food and Drug Administration (FDA) approved labeling; and
  - Initial authorization will be for no more than 12 months
- For continuation of therapy, all of the following:
  - Patient has previously received treatment with elosulfase alfa therapy; and
  - Patient has experienced a positive clinical response to elosulfase alfa therapy (e.g., improved endurance, improved functional capacity, reduced urine keratan sulfate excretion); and
  - Dosing is in accordance with the U.S. Food and Drug Administration (FDA) approved labeling; and
  - Reauthorization will be for no more than 12 months

Xenpozyme (olipudase alfa-rpcp) is medically necessary for the treatment of acid sphingomyelinase deficiency (ASMD) when all of the following criteria are met:

- For initial therapy, all of the following:
  - Diagnosis of acid sphingomyelinase deficiency (ASMD) type A/B or B confirmed by one of the following:
    - Absence or deficiency of acid sphingomyelinase (ASM) enzyme activity
    - Molecular genetic testing for mutations in the SMPD1 gene

    and
  - Presence of clinical signs and symptoms of the disease (e.g., hepatosplenomegaly, elevated transaminases, mixed dyslipidemia, abnormal pulmonary function)
  - Xenpozyme is not being used to treat central nervous system (CNS) manifestations of ASMD
  - Dosing is in accordance with the United States Food and Drug Administration approved labeling; and
  - Initial authorization will be for no more than 12 months.
- For continuation of therapy, all of the following:
  - Patient has previously received treatment with olipudase alfa therapy; and
  - Patient has experienced a positive clinical response to olipudase alfa therapy (e.g., reduced spleen volume, reduced liver volume, improved liver transaminase levels, improved lipid profile, improved pulmonary function); and
  - Dosing is in accordance with the United States Food and Drug Administration approved labeling; and
  - Reauthorization will be for no more than 12 months.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

Aldurazyme

HCPCS Code	Description
J1931	Injection, laronidase, 0.1 mg

Diagnosis Code	Description
E76.01	Hurler's syndrome
E76.02	Hurler-Scheie syndrome
E76.03	Scheie's syndrome

Elaprase

HCPCS Code	Description
J1743	Injection, idursulfase, 1 mg

Diagnosis Code	Description
E76.1	Mucopolysaccharidosis, type II

Fabrazyme

HCPCS Code	Description
J0180	Injection, agalsidase beta, 1 mg

Diagnosis Code	Description
E75.21	Fabry (-Anderson) disease

Kanuma

HCPCS Code	Description
J2840	Injection, sebelipase alfa, 1 mg
Diagnosis Code	Description
E75.5	Other lipid storage disorders

Lumizyme

HCPCS Code	Description
J0221	Injection, alglucosidase alfa, (Lumizyme), 10 mg

Diagnosis Code	Description
E74.02	Pompe disease

Mepsevii

HCPCS Code	Description
J3397	Injection, vestronidase alfa-vjbk, 1 mg

Diagnosis Code	Description
E76.29	Other mucopolysaccharidoses (includes Sly syndrome)

Naglazyme

HCPCS Code	Description
J1458	Injection, galsulfase, 1 mg

Diagnosis Code	Description
E76.29	Other mucopolysaccharidoses (includes Maroteaux-Lamy syndrome)

Nexviazyme

HCPCS Code	Description
J0219	Injection, avalglucosidase alfa-ngpt, 4 mg

Diagnosis Code	Description
E74.02	Pompe disease

Nulibry

HCPCS Code	Description
C9399	Unclassified drugs or biologicals
J3490	Unclassified drugs
J3590	Unclassified biologics

Diagnosis Code	Description
E72.10	Disorders of sulfur-bearing amino-acid metabolism, unspecified
E72.19	Other disorders of sulfur-bearing amino-acid metabolism

Revcovi

HCPCS Code	Description
J3590	Unclassified biologic

Diagnosis Code	Description
D81.31	Severe combined immunodeficiency due to adenosine deaminase deficiency

Vimizim

HCPCS Code	Description
J1322	Injection, elosulfase alfa, 1mg

Diagnosis Code	Description
E76.210	Morquio A mucopolysaccharidoses

Xenpozyme

HCPCS Code	Description
C9399	Unclassified drugs or biologicals
J3490	Unclassified drugs
J3590	Unclassified biologics

Diagnosis Code	Description
E75.241	Niemann-Pick disease type B; also applicable to ASMD type B & Chronic visceral acid sphingomyelinase deficiency
E75.244	Niemann-Pick disease type A/B; ASMD type A/B & Chronic neurovisceral acid sphingomyelinase deficiency

Background

Aldurazyme (laronidase) is a polymorphic variant of the human enzyme α-L -iduronidase that is produced by recombinant DNA technology in a Chinese hamster ovary cell line. α-L - iduronidase (glycosaminoglycan α-L - iduronohydrolase) is a lysosomal hydrolase that catalyzes the hydrolysis of terminal α-L - iduronic acid residues of dermatan sulfate and heparan sulfate. Aldurazyme therapy is to provide exogenous enzyme for uptake into lysosomes and increase the catabolism of GAG.[9]

Elaprase (idursulfase) is a formulation of idursulfase, a purified form of human iduronate-2-sulfatase, a lysosomal enzyme. Idursulfase is produced by recombinant DNA technology in a human cell line. Idursulfase is an enzyme that hydrolyzes the 2-sulfate esters of terminal iduronate sulfate residues from the glycosaminoglycans dermatan sulfate and heparan sulfate in the

lysosomes of various cell types. Elaprase is intended to provide exogenous enzyme for uptake into cellular lysosomes, leading to cellular internalization of the enzyme, targeting to intracellular lysosomes and subsequent catabolism of accumulated GAG.[10]

Fabrazyme (agalsidase beta) is a recombinant human α-galactosidase an enzyme with the same amino acid sequence as the native enzyme. α-galactosidase A catalyzes the hydrolysis of globotriaosylceramide (GL-3) and other α-galactyl-terminated neutral glycosphingolipids, such as galabiosylceramide and blood group B substances to ceramide dihexoside and galactose. Fabrazyme is intended to provide an exogenous source of α-galactosidase A in Fabry disease patients. Nonclinical and clinical studies evaluating a limited number of cell types indicate that Fabrazyme will catalyze the hydrolysis of glycosphingolipids, including GL-3.[11]

Kanuma (sebelipase alfa) is a recombinant human lysosomal acid lipase (rhLAL). Lysosomal acid lipase is a lysosomal glycoprotein enzyme that catalyzes the hydrolysis of cholesteryl esters to free cholesterol and fatty acids and the hydrolysis of triglycerides to glycerol and free fatty acids. Sebelipase alfa binds to cell surface receptors via glycans expressed on the protein and is subsequently internalized into lysosomes. Sebelipase alfa catalyzes the lysosomal hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol and free fatty acids.[12]

Lumizyme (alglucosidase alfa) is a hydrolytic lysosomal glycogen-specific enzyme encoded by the predominant of nine observed haplotypes of the human acid α-glucosidase (GAA) gene. Alglucosidase alfa is produced by recombinant DNA technology in a Chinese hamster ovary cell line. Alglucosidase alfa degrades glycogen by catalyzing the hydrolysis of α-1,4 - and α-1,6 - glycosidic linkages of lysosomal glycogen. Alglucosidase alfa provides an exogenous source of GAA. Binding to mannose-6-phosphate receptors on the cell surface has been shown to occur via carbohydrate groups on the GAA molecule, after which it is internalized and transported into lysosomes, where it undergoes proteolytic cleavage that results in increased enzymatic activity. It then exerts enzymatic activity in cleaving glycogen.[13]

Mepsevii (vestronidase alfa-vjbk) is a recombinant form of human beta-glucuronidase (GUS) and is intended to provide exogenous GUS enzyme for uptake into cellular lysosomes. Mannose - 6-phosphate (M6P) residues on the oligosaccharide chains allow binding of the enzyme to cell surface receptors, leading to cellular uptake of the enzyme, targeting to lysosomes and subsequent catabolism of accumulated GAGs in affected tissues.[22]

Naglazyme (galsulfase) is a formulation of galsulfase, which is a purified human enzyme that is produced by recombinant DNA technology in a Chinese hamster ovary cell line. Galsulfase (glycosaminoglycan N - acetylgalactosamine 4-sulfatase) is a lysosomal enzyme that catalyzes the cleavage of the sulfate ester from terminal N - acetylgalactosamine 4-sulfate residues of glycosaminoglycans (GAG), chondroitin 4 - sulfate and dermatan sulfate. Naglazyme is intended to provide an exogenous enzyme that will be taken up into lysosomes and increase the catabolism of GAG.[14]

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

Nulibry (fosdenopterin) is a cyclic pyranopterin monophosphate (cPMP) available for exogenous uptake for conversion into molybdopterin. Molybdopterin is then converted to molybdenum cofactor, which is needed for activation of molybdenum-dependent enzymes, including sulfite oxidase (SOX), an enzyme responsible for reducing levels of neurotoxic sulfites.[26]

Revcovi (elapegademase-lvlr) is a recombinant adenosine deaminase (rADA) based on bovine amino acid sequence, conjugated to monomethoxy polyethylene glycol (mPEG). rADA is manufactured in E.coli and is covalently conjugated to mPEG with a succinimidyl carbamate linker to produce methoxy polyethylene glycol recombinant adenosine deaminase (SC-PEG rADA). The approximate molecular weight of elapegademase-lvlr (SC - PEG rADA) is 113 KDa.[24]

Vimizim (elosulfase alfa) is a purified human enzyme produced by recombinant DNA technology which provides exogenous N - acetylgalactosamine-6-sulfatase. The mannose-6-phosphate-terminated oligosaccharide chains of elosulfase alfa bind to mannose-6-phosphate receptors of lysosomal cells resulting in cellular uptake of elosulfase alfa and increased catabolism of KS and C6S.[1,5]

Xenpozyme (olipudase alfa) is a recombinant hydrolytic lysosomal human acid sphingomyelinase (ASM) enzyme designed to reduce sphingomyelin (SM) accumulation in the liver, spleen, and lung of patients with acid sphingomyelinase deficiency (ASMD). It provides exogenous ASM, replacing deficient or defective ASM caused by pathogenic variants in the sphingomyelin phosphodiesterase 1 gene (SMPD1). Olipudase alfa-rpcp is not expected to cross the blood-brain barrier or modulate the CNS manifestations of ASMD.[28]

Clinical Evidence

Proven

Aldurazyme

To confirm the efficacy and safety of recombinant human α-L - iduronidase (laronidase) in patients with mucopolysaccharidosis I (MPS I), Wraith et al., conducted a randomized, double-blinded, placebo-controlled, multicenter, multinational study of 45 patients with MPS I.[16] Patients were randomized to receive either laronidase (100 U/kg, n = 22), or placebo (n = 23), intravenously each week for 26 weeks. The primary endpoints assessed were the comparison of the median change from baseline to week 26 between the groups in percentage of predicted normal forced vital capacity (FVC) and in the 6-minute walk test (6MWT) distance, using the Wilcoxon rank sum test. After 26 weeks of treatment, patients in the laronidase group showed mean improvements in the percent of predicted normal FVC (5.6 percentage point reduction (median, 3.0; p = 0.009), and 38.1 meters in the 6MWT distance (median 38.5; p = 0.066; p = 0.039, analysis of covariance) compared to placebo. Patients who received laronidase also experienced reduced hepatomegaly (20% between-group difference, p = 0.001), and urinary glycosaminoglycans (reduction of 54.1% compared to a 47.3% increase in the placebo group, p < 0.001). More severely affected patients also had improved sleep apnea/hypopnea and shoulder flexion. The authors concluded that laronidase significantly improved respiratory function and physical capacity, reduced glycosaminoglycan storage, and had a favorable safety profile.

Elaprase

Muenzer et al, conducted a randomized, double-blind, placebo-controlled, multicenter, multinational clinical trial to evaluate the safety and efficacy of recombinant human iduronate-2-sulfatase (idursulfase) in the treatment of mucopolysaccharidosis II (MPS II).[17] Patients between the ages of 5 and 31 years old (n = 96), were evenly randomized (n = 32) to receive either weekly idursulfase (0.5 mg/kg) infusions, every other week (0.5mg/kg) infusions, or placebo. The primary efficacy assessment was the comparison between the placebo and weekly infusion group from the change in baseline to week 53 in a single, two-component composite variable combining %FVC as a measure of respiratory function and 6MWT as a measure of physical functional capacity using the O'Brien procedure for analysis. Secondary efficacy variables included changes in the individual components of the composite endpoint (6MWT distance and %FVC), absolute FVC, liver and spleen volumes measured by abdominal MRI, urine GAG excretion and passive joint range of motion. Patients in the weekly and every-other-week idursulfase groups exhibited significant improvement in the composite endpoint compared to placebo (p = 0.0049 for weekly and = 0.0416 for every other week) after one year. The weekly dosing group experienced a 37-m increase in the 6-minute-walk distance (p = 0.013), a 2.7% increase in percentage of predicted forced vital capacity (p = 0.065), and a 160 mL increase in absolute forced vital capacity (p = 0.001) compared to placebo group at 53 weeks. After 53 weeks in the intent to treat population, liver volume had decreased from baseline by 25.3 ±1.6% in the idursulfase weekly group and by 24.0 ±1.7% in the idursulfase every other week group. The change in both groups was statistically significantly greater than the change in the placebo group (-0.8 ±1.6%, p < 0.0001 compared to either idursulfase group). At Week 53, the GAG levels in the idursulfase groups were significantly different than that of the placebo group (p < 0.0001 for either group compared to placebo). Idursulfase was generally well tolerated, but infusion reactions did occur. The authors concluded that weekly infusions of idursulfase produced a clinical benefit based on the significant improvements in the two-component composite endpoint, 6MWT distance and %FVC compared to placebo.

Fabrazyme

A multicenter, randomized, double-blind, placebo-controlled study was conducted to assess the efficacy of agalsidase beta to delay the onset of composite clinical outcome of renal, cardiovascular, and cerebrovascular events, and death in patients with advanced Fabry disease.[18] Patients (n = 82), were randomized (2:1 treatment-to-placebo) to receive either an intravenous infusion of agalsidase beta (1mg/kg) or placebo every 2 weeks for up to 35 months. The primary endpoint was the time to first clinical event (renal, cardiac, or cerebrovascular event, or death). Thirteen (42%) of the 31 patients in the placebo group, and 14 (27%) of the 51 patients in the agalsidase-beta group experienced clinical events. Primary intention-to-treat analysis that

adjusted for an imbalance in baseline proteinuria showed that, compared with placebo, agalsidase beta delayed the time to first clinical event (hazard ratio, 0.47 [95% CI, 0.21 to 1.03]; p = 0.06). Secondary analyses of protocol-adherent patients showed similar results (hazard ratio, 0.39 [CI, 0.16 to 0.93]; p = 0.034). Ancillary subgroup analyses found larger treatment effects in patients with baseline estimated glomerular filtration rates greater than 55 mL/min per 1.73 m^2 (hazard ratio, 0.19 [CI, 0.05 to 0.82]; p = 0.025) compared with 55 mL/min per 1.73 m^2 or less (hazard ratio, 0.85 [CI, 0.32 to 2.3]; p = 0.75) (formal test for interaction, p = 0.09). Most treatment-related adverse events were mild or moderate infusion-associated reactions, reported by 55% of patients in the agalsidase-beta group and 23% of patients in the placebo group. The authors concluded that therapy with agalsidase beta slowed the progression to the composite clinical outcome of renal, cardiac, and cerebrovascular complications and death compared with placebo in patients with advanced Fabry disease. The authors recommend therapeutic intervention before irreversible organ damage to provide greater clinical benefit.

Kanuma

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

Lumizyme

A randomized, double-blind, placebo-controlled, multicenter study was conducted to determine the safety and efficacy of alglucosidase alfa (GAA) for the treatment of late-onset Pompe disease.[20] Ninety patients, 8 years of age or older, who were ambulatory, not dependent on invasive ventilation, were randomly assigned 2:1 to receive bi-weekly infusions of GAA (20mg/kg, n = 60) or placebo (n = 30). Co-primary efficacy end points were meters walked on the 6-minute walk test and percentage of the predicted FVC in the upright position. Secondary and tertiary efficacy end points included changes in the percentage of the predicted QMT leg score and QMT arm score, maximum inspiratory pressure, and maximum expiratory pressure. By 78 weeks, treatment with GAA had significantly increased both the distance walked on the 6-minute walk test and the percentage of the predicted FVC. The GAA group had a mean increase of 25.1 m on the 6-minute walk test (the average baseline was 332.2 m), whereas the placebo group had a decrease of 3.0 m (the average baseline was 317.9 m), for an estimated differential treatment effect of 28.1 m (p = 0.03). The estimated change in FVC, expressed as a percentage of each patient's predicted value, was an increase of 1.2 percentage points for the patients who received GAA and a decrease of 2.2 percentage points for the patients who received placebo, for an estimated treatment effect of 3.4 percentage points (p = 0.006). Patients in the two groups had similar frequencies of adverse events, serious adverse events, treatment-related adverse events, and infusion associated reactions. The authors concluded that, in this study population, treatment with alglucosidase alfa was associated with improved walking distance and stabilization of pulmonary function over an 18-month period.

Naglazyme

The efficacy and safety of recombinant human arylsulfatase B (rhASB) for the treatment of mucopolysaccharidosis type VI (MPS VI), was confirmed in a Phase 3, randomized, double-blind, placebo-controlled, multicenter, multinational study.[21] Thirty-

nine patients with MPS VI were randomized in a 1:1 ratio to receive weekly intravenous infusions of either rhASB 1mg/kg or placebo for 24 consecutive weeks. After 24 weeks, all patients completing treatment were enrolled in the open-label extension. The primary efficacy endpoint variable, the distance walked in a 12-minute walk test (12MWT), provided a measure of endurance. Secondary efficacy endpoints included the 3-minute stair climb (3MSC) and urine GAG levels. Tertiary end points included: (1) assessments of joint pain, joint stiffness, and physical energy level; (2) assessment of joint range of motion; and (3) assessment of hand dexterity as evidenced by number of coins picked up in 1 minute. After 24 weeks, patients receiving rhASB walked on average 92 meters (m) more in the 12MWT (p = 0.025) and 5.7 stairs per minute more 3MSC (p = 0.053) than patients receiving placebo. Continued improvement was observed during the extension study. Urinary GAG declined by -27 ±18 µg/mg more with rhASB than placebo (p < .001). Infusions were generally safe and well tolerated. Patients exposed to drug experienced positive clinical benefit despite the presence of antibody to the protein. The authors concluded that rhASB significantly improved endurance, reduced urine GAG levels, and had an acceptable safety profile.

Nexviazyme

The efficacy and safety of avalglucosidase alfa-ngpt for the treatment of late onset Pompe disease was evaluated in a randomized, double-blinded, multinational, multicenter trial (NCT02782741). Efficacy and safety was compared to alglucosidase alfa. 100 treatment-naïve patients were randomized in a 1:1 ratio, based on forced vital capacity (FVC), age, gender, and country, to receive 20 mg/kg of avalglucosidase alfa-ngpt or alglucosidase alfa administered once every two weeks for 49 weeks. The trial included an open label, long-term, follow-up of up to 5 years, in which patients were switched to avalglucosidase alfa-ngpt treatment. The primary endpoint was the change in FVC (% predicted) in the upright position from baseline to week 49. Secondary endpoint was the change in total walking distance in 6 minutes (6-minute walk test) from baseline to week 49. At week 49, the least squares (LS) mean change in FVC was 2.9% (avalglucosidase alfa-ngpt) and 0.5% (alglucosidase alfa), with an estimated treatment difference of 2.4% (95% CI: -0.1, 5) favoring avalglucosidase alfa-ngpt [noninferiority margin of 1.1% (p = 0.0074), statistical superiority was not achieved (p = 0.06)]. Secondary endpoint had an estimated treatment difference of 30 meters (95% CI: 1.3, 58.7) favoring avalglucosidase alfa-ngpt (p = 0.04). [27]

Nulibry

The safety and efficacy of fosdenopterin was evaluated in three clinical studies (NCT02047461, NCT02629393) comparing data from a natural history study. A total of 13 patients received fosdenopterin and recombinant Escherichia coli-derived cPMP (rcCMP) in the three trials. Efficacy was assessed by comparison of overall survival (OS) in pediatric patients treated with either Nulibry or rcCMP to an untreated natural history cohort of pediatric patients with genetically confirmed MoCD Type A (genotype matched to treated patients) (n = 18). Authors found that patients treated with fosdenopterin or rcPMP had an improved overall survival compared to the untreated, genotype-matched, historical control group (HR 0.18; 95% CI 0.04, 0.72). Additionally, treatment with fosdenopterin resulted in reduction in urine concentration of SSC in patients with MoCD Type A. Reduction was sustained with long-term treatment over 48 months.[26]

Revcovi

The safety and efficacy of elapegademase-lvlr was evaluated in a phase 3, open-label, multicenter, single-arm, one-way crossover study. The study consisted of three phases: Adagen Lead-in Phase (minimum of 3 weeks), the Revcovi Treatment Phase (weeks 1 through 21) and followed by the Revcovi Maintenance Phase. The efficacy endpoints evaluated included trough dAXP level, trough plasma ADA activity and immune status. Five of six patients reached the 21-week endpoint of the Treatment Phase. These patients (except for one value in a patient at Treatment Week 47) had erythrocyte dAXP concentration equal to or below 0.02 mmol/L. These patients had trough plasma ADA activity equal to or above 15 mmol/hr/L at 88/89 time points and maintained metabolic detoxification for at least 2 years under Revcovi treatment. Patients achieved through plasma ADA activity above 30 mmol/hr/L by week 5, except for one patient who achieved this level at week 1. The mean trough plasma ADA activity for patients receiving Revcovi at a normalized dose of 0.2 mg/kg/week were 34.3 ±6.6 mmol/hr/L. The same patients had a mean trough plasma ADA activity of 14.2 ±5.1 mmol/hr/L when treated with Adagen at a normalized dose of 30 U/kg/week during the Lead-in Phase of the study. For these three patients who completed the primary endpoint or 21 weeks of treatment and received Revcovi for over 135 weeks, a positive trend between high trough plasma ADA activity and increased total lymphocyte counts was observed.[24]

Another study to evaluate the safety, efficacy and PK of Revcovi in patients with ADA-SCID included two phases, and evaluation and dose maintenance period. A total of four patients were enrolled in the study: two patients, who were on Adagen treatment within 4 weeks before entering the study, received a first dose of Revcovi that was calculated to be equivalent their prior Adagen dose. One patient, who did not receive Adagen within four weeks prior to entering the study. Over the dose adjustment

phase of the study, the dose was titrated to meet criteria for dAXP level (equal to or below 0.02 mmol/L) and adequate trough ADA activity. The fourth patient was dosed with Revcovi at 0.4 mg/kg weekly for 16 weeks. All four of the patients in Study 2 achieved and maintained detoxification throughout their participation in the Treatment Phase of 21 weeks. Serum ADA activity increased after administering REVCOVI for all four patients, with three patients achieving activity level over 15 mmol/hr/L during the Dose Maintenance Period. Total lymphocyte counts and B -/T -/NK - lymphocyte subset counts for three patients increased from screening to Day 15 during dose adjustment and were stable or increasing during the Maintenance Period.[24]

Vimizim

In an ad hoc analysis of the primary phase 3 trial, Schweighardt et al examined the immunogenicity of elosulfase alfa and evaluated the effects of antibody formation on the overall efficacy and safety in patients with Morquio A syndrome.[7] During the trial, all patients treated with elosulfase alfa developed anti-elosulfase alfa antibodies (TAb). Those patients who received the once weekly therapy (QW) tested positive at a faster rate (all by week 4) versus the every other week (QOW) patients (all by week 16). The mean TAb titers by week 24 were similar in both dosing cohorts. About 20% of all study participants tested positive for TAb at baseline. Neutralizing antibodies (NAb) to elosulfase alfa, which inhibit its interaction to the mannose-6-phosphate receptor, and anti-elosulfase alfa IgE were also assayed throughout the trial. A majority (87%) of patients from the QW cohort and 80% from the QOW cohort tested positive for NAb by week 24 of the study. NAb is not of concern to efficacy, however, since elosulfase alfa is not active in the neutral pH of blood but is active in the acidic pH of the lysosome, where NAb cannot penetrate, and thus is not a factor in hindering efficacy. Anti-elosulfase alfa IgE was detected in less than 10% of all patients receiving elosulfase alfa regimens: 8.6% of patients in the QW cohort and 6.8% in the QOW cohort. During the trial, however, most patients with serious adverse events (13 patients), including 3 patients with drug-related serious events of hypersensitivity, vomiting, and anaphylaxis, did not test positive for antidrug IgE. Regardless of TAb titers or NAb positivity, both dosing cohorts had a similar percentage of change in urinary keratin sulfate levels. There were no associations between TAb titers or NAb positivity and patient efficacy outcomes in either the QW or QOW groups, as measured by the 6-min walk test. The authors concluded that immunogenicity was not associated with reduced treatment effect of elosulfase alfa in patients with Morquio A syndrome.

To assess efficacy and safety of elosulfase alfa, researchers conducted a 24-week randomized, double-blind, placebo-controlled phase 3 trial (MOR-004) involving 176 patients (5 to 57 years of age) with mucopolysaccharidosis type IV A (Morquio A syndrome).[1,2,6] Patients were randomized (1:1:1) to receive elosulfase alfa 2.0 mg/kg/every other week (QOW), elosulfase alfa 2.0 mg/kg/week (weekly), or placebo for 24 weeks. The primary outcome measured was 6-min walk test (6MWT) distance. Secondary efficacy outcomes assessed were 3-min stair climb test (3MSCT) followed by change in urine keratan sulfate (KS). Patient safety was also evaluated. At baseline, patients could walk 30 to 325 m in 6 minutes; 82% had a history of musculoskeletal conditions including knee deformity (52%), kyphosis (31%), hip dysplasia (22%), prior spinal fusion surgery (22%), and arthralgia (20%). The estimated mean effect at week 24 on 6MWT (primary endpoint) versus placebo was 22.5 m (95% CI 4.0, 40.9; p = 0.017) for weekly and 0.5 m (95% CI -17.8, 18.9; p = 0.954) for QOW. The estimated mean effect on 3MSCT (secondary endpoint) was 1.1 stairs/min (95% CI -2.1, 4.4; p = 0.494) for weekly and -0.5 stairs/min (95% CI -3.7, 2.8; p = 0.778) for QOW. Normalized urine KS was reduced at 24 weeks in both regimens; however, the clinical significance of this finding has not been established. In the weekly dose group, 22.4% of patients had adverse events leading to an infusion interruption/discontinuation requiring medical intervention (only 1.3% of all infusions in this group), however, none of the adverse events led to permanent treatment discontinuation. No significant improvement in endurance in the 3MSCT rate was observed between these 2 groups. The performance (3MSCT rate or 6MWT) of patients receiving elosulfase alfa QOW did not differ significantly from placebo. Researchers concluded that these regimens were shown to provide generally safe enzyme replacement therapy (ERT) for patients with Morquio A syndrome. In MOR-005, patients who participated in the placebo-controlled trial were eligible to continue treatment in an open-label extension trial to evaluate the long-term safety and efficacy of elosulfase alfa.[1,6] One hundred seventy-three of 176 patients enrolled in the extension trial in which patients received elosulfase alfa 2 mg/kg/wk (n = 86) or Vimizim 2 mg/kg/QOW (n = 87). In patients who continued to receive elosulfase alfa 2 mg/kg/wk for another 48 weeks (for a total of 72-week exposure), no further improvement in walking ability beyond the first 24 weeks was observed. Researchers concluded that elosulfase alfa may present as new treatment for Morquio A patients who have currently no medical care option other than symptomatic therapy of disease complications. Additionally, the study population of the trial can be considered representative of the general Morquio A population.

Xenpozyme

The efficacy of Xenpozyme for the treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) has been evaluated in 3 trials in patients with ASMD.[28]

Trial 1 was a randomized, double-blinded, placebo-controlled, repeat-dose trial in 31 adult patients with ASMD (clinical diagnosis consistent with ASMD type B and A/B). Patients received either Xenpozyme or placebo. Key efficacy endpoints included assessment of % predicted diffusion capacity of the lungs for carbon monoxide (DLco), spleen volume, liver volume, and platelet count. At week 52, an increase of 20.9% in the mean percent change in % predicted DLco was observed in the Xenpozyme-treated patients compared to the placebo-treated patients ($p = 0.0003$). A reduction in spleen volume of 39.4% was observed in the Xenpozyme-treated patients compared to the placebo-treated patients ($p < 0.0001$). A 24.7% decrease in mean liver volume and a 15.6% increase in mean platelet count were also noted in the Xenpozyme-treated patients compared to the placebo-treated patients at week 52 ($p < 0.0001$ and $p = 0.0280$, respectively).[28,31]

Trial 2 was an open-label, repeated-dose trial of Xenpozyme in 8 pediatric patients aged < 18 years with a clinical diagnosis consistent with ASMD type B and A/B. Exploratory efficacy endpoints related to organomegaly, pulmonary and liver functions, and linear growth were evaluated at week 52. Treatment with Xenpozyme resulted in improvements in mean percent change in % predicted DLco, spleen and liver volumes, platelet counts, and linear growth progression (as measured by height Z-scores) at week 52 as compared to baseline. Refer to the drug label for full results.[28,32]

Additionally, the 8 pediatric patients 2 to < 12 years of age from Trial 2 continued treatment in an open label long term trial (Trial 3) and were treated with Xenpozyme for 2.5 to 3.2 years. Efficacy analyses showed continued improvements in the 3 patients evaluated for % predicted DLco, 6 patients evaluated for platelet counts, and all 8 patients evaluated for spleen and liver volumes, compared to baseline, during the additional 6 months extension. In addition, the height Z-score increased by 1.3 from baseline when evaluated through 24 months of Xenpozyme treatment.[28]

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Aldurazyme (laronidase) is indicated for patients with Hurler and Hurler-Scheie forms of Mucopolysaccharidosis I (MPS I) and for patients with the Scheie form who have moderate to severe symptoms. The risks and benefits of treating mildly affected patients with the Scheie form have not been established. Aldurazyme has been shown to improve pulmonary function and walking capacity. Aldurazyme has not been evaluated for effects on the central nervous system manifestations of the disorder.[9]

Elaprase (idursulfase) is indicated for patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II). Elaprase has been shown to improve walking capacity in patients 5 years and older. In patients 16 months to 5 years of age, no data are available to demonstrate improvement in disease-related symptoms or long-term clinical outcome; however, treatment with Elaprase has reduced spleen volume similarly to that of adults and children 5 years of age and older. The safety and efficacy of Elaprase have not been established in pediatric patients less than 16 months of age.[10]

Fabrazyme (agalsidase beta) is indicated for use in patients with Fabry disease. Fabrazyme reduces globotriaosylceramide (GL-3) deposition in capillary endothelium of the kidney and certain other cell types.[11]

Kanuma is indicated for the treatment of patients with a diagnosis of Lysosomal Acid Lipase (LAL) deficiency.[12]

Lumizyme (alglucosidase alfa) is a hydrolytic lysosomal glycogen-specific enzyme indicated for patients with Pompe disease (acid α-glucosidase (GAA) deficiency).[13]

Mepsevii (vestronidase alfa-vjbk) is indicated in pediatric and adult patients for the treatment of Mucopolysaccharidosis type VII (MPS VII, Sly syndrome). The effect of Mepsevii on the central nervous system manifestations of MPS VII has not been determined.[22]

Naglazyme (galsulfase) is indicated for patients with Mucopolysaccharidosis VI (MPS VI, Maroteaux-Lamy syndrome). Naglazyme has been shown to improve walking and stair-climbing capacity.[14]

Nexviazyme (avalglucosidase alfa-ngpt) is indicated for the treatment of patients 1 year of age and older with late-onset Pompe disease [lysosomal acid alpha-glucosidase (GAA) deficiency].[27]

Nulibry (fosdenopterin) is indicated to reduce the risk of mortality in patients with molybdenum cofactor deficiency (MoCD) Type A.[26]

Revcovi (elapegademase-lvlr) is indicated for the treatment of adenosine deaminase severe combined immune deficiency (ADA-SCID) in pediatric and adult patients.[24]

Vimizim (elosulfase alfa) is a hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme FDA-labeled for patients with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome).[1]

Xenpozyme (olipudase alfa) is indicated for the treatment of non-central nervous system (non-CNS) manifestations of acid sphingomyelinase deficiency (ASMD) in adult and pediatric patients.[28]

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Policy History/Revision Information

Date	Summary of Changes
12/01/2022	**Coverage Rationale** • Revised list of applicable medical therapies for enzyme deficiency products; added Xenpozyme™ (olipudase alfa-rpcp) • Added language to indicate Xenpozyme is medically necessary for the treatment of acid sphingomyelinase deficiency (ASMD) when all of the following criteria are met: *Initial Therapy* ○ Diagnosis of acid sphingomyelinase deficiency (ASMD) type A/B or B confirmed by one of the following: ▪ Absence or deficiency of acid sphingomyelinase (ASM) enzyme activity ▪ Molecular genetic testing for mutations in the SMPD1 gene ○ Presence of clinical signs and symptoms of the disease (e.g., hepatosplenomegaly, elevated transaminases, mixed dyslipidemia, abnormal pulmonary function) ○ Xenpozyme is not being used to treat central nervous system (CNS) manifestations of ASMD ○ Dosing is in accordance with the U.S. FDA approved labeling

Date	Summary of Changes
	○ Initial authorization will be for no more than 12 months *Continuation of Therapy* ○ Patient has previously received treatment with olipudase alfa therapy ○ Patient has experienced a positive clinical response to olipudase alfa therapy (e.g., reduced spleen volume, reduced liver volume, improved liver transaminase levels, improved lipid profile, improved pulmonary function) ○ Dosing is in accordance with the U.S. FDA approved labeling ○ Reauthorization will be for no more than 12 months Applicable Codes *Xenpozyme* (new to policy) • Added HCPCS codes C9399, J3490, and J3590 • Added ICD-10 diagnosis codes E75.241 and E75.244 Supporting Information • Updated *Background*, *Clinical Evidence*, *FDA*, and *References* sections to reflect the most current information • Archived previous policy version CS2022D0052V

Instructions for Use

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