Medical Therapies for Enzyme Deficiencies

Policy Number: 2026D0052AF
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➲ Instructions for Use

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Related Commercial Policies
- Intravenous Enzyme Replacement Therapy (ERT) for Gaucher Disease
- Medical Benefit Therapeutic Equivalent Medications – Excluded Drugs
- Provider Administered Drugs – Site of Care

Community Plan Policy
- Medical Therapies for Enzyme Deficiencies

Medicare Advantage Policy
- Medicare Part B Step Therapy Programs

Coverage Rationale

➲ See Benefit Considerations

This policy refers to the following medical therapies for enzyme deficiency products:
- Aldurazyme® (laronidase)
- Avlayah™ (tividenofusp alfa-eknm)
- Elaprase® (idursulfase)
- Elfabrio® (pegunigalsidase alfa-iwxj)
- Fabrazyme® (agalsidase beta)
- Kanuma® (sebelipase alfa)
- Lamzede® (velmanase alfa-tycv)
- Loargys® (pegzilarginase-nbln)
- Lumizyme® (alglucosidase alfa)
- Mepsevii® (vestronidase alfa-vjbk)
- Naglazyme® (galsulfase)
- Nexviazyme™ (avalglucosidase alfa-ngpt)
- Nulibry® (fosdenopterin)
- Pombiliti™ (cipaglucosidase alfa-atga)
- Revcovi® (elapegademase-lvlr)
- Vimizim® (elosulfase alfa)
- Xenpozyme™ (olipudase alfa-rpcp)

Elfabrio® is typically excluded from coverage. Coverage reviews may be in place if required by law or the benefit plan. Refer to the Medical Benefit Drug Policy titled Medical Benefit Therapeutic Equivalent Medications – Excluded Drugs and the corresponding excluded drug list with preferred alternatives.

Note: For requests that require medical necessity review, also refer to the Drug-Specific Criteria section below. (For Medicare reviews, refer to the CMS section.*)

Coverage for Aldurazyme, Avlayah, Elaprase, Fabrazyme, Kanuma, Lamzede, Loargys, Lumizyme, Mepsevii, Naglazyme, Nexviazyme, Nulibry, Pombiliti, Revcovi, Vimizim, and Xenpozyme is contingent on criteria in the Drug-Specific Criteria section below.

Drug-Specific Criteria

Aldurazyme (laronidase) is proven for the treatment of mucopolysaccharidosis I (MPS I). Aldurazyme is medically necessary when the following additional criteria are met:
- For **initial therapy**, **all** of the following:
  - Diagnosis of any of the MPS I syndromes confirmed by **one** of the following:
    - Hurler variant (severe mucopolysaccharidosis I; also MPS IH); **or**

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        - Hurler-Scheie variant (attenuated mucopolysaccharidosis I; also MPS IHS); **or**
        - Scheie variant (attenuated mucopolysaccharidosis I; also MPS IS)

      and
    - Diagnosis of MPS I is confirmed by **one** of the following:
        - Deficiency or absence of fibroblast or leukocyte enzyme activity of alpha-L-iduronidase enzyme activity; **or**
        - 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 FDA-approved labeling; **and**
    - Reauthorization will be for no more than 12 months

Avlayah (tividenofusp alfa) is proven for the treatment of neurologic manifestations of Hunter syndrome (Mucopolysaccharidosis type II, MPS II) . Avlayah is medically necessary when the following additional criteria are met:

- For **initial therapy**, **all** of the following:
    - Diagnosis of MPS II confirmed by **one** of the following:
        - Deficiency in iduronate 2-sulfatase enzyme activity as measured in fibroblasts or leukocytes combined with normal enzyme activity level of another sulfatase; **or**
        - 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**
    - Avlayah is not being used to treat MPS II in combination with Elaprase; **and**
    - Dosing is in accordance with the 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 tividenofusp alfa; **and**
    - Patient has experienced a positive clinical response to tividenofusp alfa therapy (e.g., improved hearing, improved functional capacity, improved neurological symptoms, reduced spleen volume, reduced urine glycosaminoglycan excretion, etc.); **and**
    - Avlayah is not being used to treat MPS II in combination with Elaprase; **and**
    - Dosing is in accordance with the FDA-approved labeling; **and**
    - Reauthorization will be for no more than 12 months

Elaprase (idursulfase) is proven for the treatment of mucopolysaccharidosis II (MPS II, Hunter syndrome). Elaprase is medically necessary when the following additional criteria are met:

- For **initial therapy**, **all** of the following:
    - Diagnosis of MPS II confirmed by **one** of the following:
        - Deficiency in iduronate 2-sulfatase enzyme activity as measured in fibroblasts or leukocytes combined with normal enzyme activity level of another sulfatase; **or**
        - 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**
    - Elaprase is not being used to treat MPS II in combination with Avlayah; **and**
    - Dosing is in accordance with the 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 glycosaminoglycan excretion, etc.); **and**
    - Elaprase is not being used to treat MPS II in combination with Avlayah; **and**
    - Dosing is in accordance with the FDA-approved labeling; **and**

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- Reauthorization will be for no more than 12 months

Elfabrio (pegunigalsidase alfa-iwxj) is proven for the treatment of adults with confirmed Fabry disease. Elfabrio is medically necessary when the following additional criteria are met:

- For **initial therapy**, **all** of the following:
  - Diagnosis of Fabry disease as confirmed by **one** of 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; **or**
    - 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/hypohidrosis, renal disease, exercise/heat/cold intolerance, etc.); **and**
  - Patient is **not** receiving Elfabrio in combination with another disease-modifying therapy used for the treatment of Fabry disease [e.g., Fabrazyme (agalsidase beta), Galafold (migalastat)]; **and**
  - Dosing is in accordance with the 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 pegunigalsidase alfa-iwxj therapy; **and**
  - Patient has experienced a positive clinical response to pegunigalsidase alfa-iwxj therapy (e.g., improved renal function, reduction in mean plasma GL-3 levels, decreased GL-3 inclusions, etc.); **and**
  - Patient is **not** receiving Elfabrio in combination with another disease-modifying therapy used for the treatment of Fabry disease [e.g., Fabrazyme (agalsidase beta), Galafold (migalastat)]; **and**
  - Dosing is in accordance with the FDA-approved labeling; **and**
  - Reauthorization will be for no more than 12 months

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

- For **initial therapy**, **all** of the following:
  - Diagnosis of Fabry disease as confirmed by **one of** 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; **or**
    - 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/hypohidrosis, renal disease, exercise/heat/cold intolerance, etc.); **and**
  - Patient is **not** receiving Fabrazyme in combination with another disease-modifying therapy used for the treatment of Fabry disease [e.g., Elfabrio (pegunigalsidase alfa-iwxj), Galafold (migalastat)]; **and**
  - Dosing is in accordance with the 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**
  - Patient is **not** receiving Fabrazyme in combination with another disease-modifying therapy used for the treatment of Fabry disease [e.g., Elfabrio (pegunigalsidase alfa-iwxj), Galafold (migalastat)]; **and**
  - Dosing is in accordance with the FDA-approved labeling; **and**
  - Reauthorization will be for no more than 12 months

Kanuma (sebelipase alfa) is proven for the treatment of lysosomal acid lipase deficiency [LAL-D, Wolman disease (WD), cholesteryl ester disease (CESD)]. Kanuma is medically necessary when the following additional 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** of the following:
    - Absence or deficiency lysosomal acid lipase activity by dried blood spot test; **or**
    - 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 FDA-approved labeling; **and**

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- 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 FDA-approved; **and**
  - Reauthorization will be for no more than 12 months

Lamzede (velmanase alfa-tycv) is proven for the treatment of alpha-mannosidosis. Lamzede is medically necessary when the following additional criteria are met:

- For **initial therapy**, **all** of the following:
  - Diagnosis of alpha-mannosidosis confirmed by **one** of the following:
    - Absence or deficiency (< 10% of the lab specific normal mean) of alpha-Mannosidase enzyme activity; **or**
    - Molecular genetic testing for mutations in the *MAN2B1* gene

    and
  - Presence of clinical signs and symptoms of the disease (e.g., hepatosplenomegaly, skeletal abnormalities, ataxia, intellectual disability, hearing loss); **and**
  - Lamzede (velmanase alfa-tycv) is not being used to treat central nervous system (CNS) manifestations of alpha-mannosidosis; **and**
  - Dosing is in accordance with the 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 Lamzede (velmanase alfa-tycv) therapy; **and**
  - Patient has experienced a positive clinical response to Lamzede (velmanase alfa-tycv) therapy (e.g., improved motor function, improved pulmonary function); **and**
  - Dosing is in accordance with the FDA-approved labeling; **and**
  - Reauthorization will be for no more than 12 months

Loargys (pegzilarginase) is proven for the treatment of hyperargininemia. Loargys is medically necessary when the following additional criteria are met:

- For **initial therapy**, **all** of the following:
  - Diagnosis of hyperargininemia (arginase 1 deficiency) confirmed by **one** of the following:
    - Absence or deficiency of arginase 1 enzyme activity; **or**
    - Genetic variants in the ARG1 gene

    and
  - Presence of clinical signs and symptoms of the disease (e.g., loss of motor skills, intellectual disability, developmental delay); **and**
  - Dosing is in accordance with the 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 pegzilarginase therapy; **and**
  - Patient has experienced a positive clinical response to pegzilarginase therapy (e.g., improved motor function, improved pulmonary function); **and**
  - Dosing is in accordance with the FDA-approved labeling; **and**
  - Reauthorization will be for no more than 12 months

Lumizyme (alglucosidase alfa) is proven for the treatment of Pompe disease. Lumizyme is medically necessary when the following additional 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** of the following:
      - Absence or deficiency (< 1% of the lab specific normal mean) of acid alpha-glucosidase (GAA) activity in skin fibroblasts; **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**
    - Patient is **not** receiving Lumizyme in combination with another disease-modifying enzyme therapy used for the treatment of Pompe disease [e.g., Nexviazyme (avalglucosidase alfa-ngpt), Pombiliti (cipaglucosidase alfa-atga)]; **and**

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        - Dosing is in accordance with the 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) of acid alpha-glucosidase (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**
        - Patient is **not** receiving Lumizyme in combination with another disease-modifying enzyme therapy used for the treatment of Pompe disease [e.g., Nexviazyme (avalglucosidase alfa-ngpt), Pombiliti (cipaglucosidase alfa-atga)]; **and**
        - Dosing is in accordance with the 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**
    - Patient is **not** receiving Lumizyme in combination with another disease-modifying enzyme therapy used for the treatment of Pompe disease [e.g., Nexviazyme (avalglucosidase alfa-ngpt), Pombiliti (cipaglucosidase alfa-atga)]; **and**
    - Dosing is in accordance with the FDA-approved labeling; **and**
    - Reauthorization will be for no more than 12 months

Mepsevii (vestronidase alfa-vjbk) is proven for the treatment of mucopolysaccharidosis VII (MPS VII, Sly syndrome). Mepsevii is medically necessary when the following additional criteria are met:

- For **initial therapy**, **all** of the following:
    - Diagnosis of mucopolysaccharidosis VII confirmed by **one** of the following:
        - Absence or deficiency of fibroblast or leukocyte enzyme activity of beta glucuronidase; **or**
        - 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 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 FDA-approved labeling; **and**
    - Reauthorization will be for no more than 12 months

Naglazyme (galsulfase) is proven for the treatment of mucopolysaccharidosis VI (MPS VI, Maroteaux-Lamy syndrome). Naglazyme is medically necessary when all of the following additional criteria are met:

- For **initial therapy**, **all** of the following:
    - Diagnosis of mucopolysaccharidosis VI confirmed by **one** 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 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**

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- Dosing is in accordance with the 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** of the following:
    - Absence or deficiency (< 40% of the lab specific normal mean) of acid alpha-glucosidase (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**
  - Patient is **not** receiving Nexviazyme in combination with another disease-modifying enzyme therapy used for the treatment of Pompe disease [e.g., Lumizyme (alglucosidase alfa), Pombiliti (cipaglucosidase alfa-atga)]; **and**
  - Dosing is in accordance with the 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 alfa-ngpt therapy; **and**
  - Patient has experienced a positive clinical response to avalglucosidase alfa-ngpt therapy (e.g., improved respiratory/cardiac function, improved endurance, etc.); **and**
  - Patient is **not** receiving Nexviazyme in combination with another disease-modifying enzyme therapy used for the treatment of Pompe disease [e.g., Lumizyme (alglucosidase alfa), Pombiliti (cipaglucosidase alfa-atga)]; **and**
  - Dosing is in accordance with the FDA-approved labeling; **and**
  - Reauthorization will be for no more than 12 months

Nulibry (fosdenopterin) is proven for the treatment of molybdenum cofactor deficiency (MoCD) type A. Nulibry is medically necessary when all of the following additional criteria are met:

- For **initial therapy**, **all** of the following:
  - Diagnosis of molybdenum cofactor deficiency (MoCD) type A confirmed by **one** of the following:
    - Absence or deficiency of sulfite oxidase enzyme activity in fibroblasts; **or**
    - Molecular genetic testing for mutations in the *MOCS1* gene

    and
  - Presence of clinical signs and symptoms of the disease (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 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 fosdenopterin therapy; **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 FDA-approved labeling; **and**
  - Reauthorization will be for no more than 12 months

Pombiliti (cipaglucosidase alfa-atga) is proven for the treatment of late-onset Pompe disease. Pombiliti 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** of the following:
    - Absence or deficiency (< 40% of the lab specific normal mean) of acid alpha-glucosidase (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**
  - Provider attests that the patient is not improving on their current enzyme replacement therapy (ERT) (e.g., Lumizyme, Nexviazyme) for the treatment of late-onset Pompe disease and this therapy will be stopped; **and**
  - Patient weighs ≥ 40kg; **and**

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- Prescribed in combination with oral Opfolda (miglustat); **and**
- Patient is **not** receiving Pombiliti in combination with another disease-modifying enzyme therapy used for the treatment of Pompe disease [e.g., Lumizyme (alglucosidase alfa), Nexviazyme (avalglucosidase alfa-ngpt)]; **and**
- Dosing is in accordance with the 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 Pombiliti therapy; **and**
  - Patient has experienced a positive clinical response to Pombiliti plus Opfolda therapy (e.g., improved respiratory/cardiac function, improved endurance, etc.); **and**
  - Continues to be prescribed in combination with Opfolda (miglustat); **and**
  - Patient is **not** receiving Pombiliti in combination with another disease-modifying enzyme therapy used for the treatment of Pompe disease [e.g., Lumizyme (alglucosidase alfa), Nexviazyme (avalglucosidase alfa-ngpt)]; **and**
  - Dosing is in accordance with the FDA-approved labeling; **and**
  - Reauthorization will be for no more than 12 months

Revcovi (elapegademase-lvlr) is proven for the treatment of adenosine deaminase severe combined immune deficiency (ADA-SCID). Revcovi is medically necessary when the following additional criteria are met:

- For **initial therapy**, **all** of the following:
  - Diagnosis of ADA-SCID; **and**
  - Deficiency of adenosine deaminase is confirmed by **one** of the following:
    - Deficiency or absence of ADA in plasma, lysed erythrocytes, fibroblasts (cultured from amniotic fluid), or chorionic villi; **or**
    - Increase in deoxyadenosine triphosphate (dATP) levels in erythrocyte lysates compared to laboratory standard; **or**
    - Decrease in ATP concentration in erythrocytes; **or**
    - Molecular genetic confirmation of mutations in both alleles of the *ADA1* gene; **or**
    - 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); **or**
    - Patient has failed HCT; **or**
    - Patient is awaiting HCT

    and
  - Dosing is in accordance with the 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 FDA-approved labeling; **and**
  - Reauthorization will be for no more than 12 months

Vimizim (elosulfase alfa) is proven for the treatment of mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome). Vimizim is medically necessary when all of the following additional criteria are met:

- For **initial therapy**, **all** of the following:
  - Diagnosis of Morquio A syndrome confirmed by **one** of the following:
    - Absence or deficiency of fibroblast or leukocyte GALNS enzyme activity; **or**
    - 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 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 FDA-approved labeling; **and**
  - Reauthorization will be for no more than 12 months

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Xenpozyme (olipudase alfa-rpcp) is proven for the treatment of acid sphingomyelinase deficiency (ASMD). Xenpozyme is medically necessary when all of the following additional 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; **or**
    - 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); **and**
  - Xenpozyme is not being used to treat central nervous system (CNS) manifestations of ASMD; **and**
  - Dosing is in accordance with the 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 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 FDA-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 the member specific benefit plan document 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

Avlayah

HCPCS Code	Description
J1757	Injection, tividenofusp alfa-eknm, 1 mg

Diagnosis Code	Description
E76.1	Mucopolysaccharidosis, type II

Elaprase

HCPCS Code	Description
J1743	Injection, idursulfase, 1 mg

Diagnosis Code	Description
E76.1	Mucopolysaccharidosis, type II

Elfabrio

HCPCS Code	Description
J2508	Injection, pegunigalsidase alfa-iwxj, 1 mg

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

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

Lamzede

HCPCS Code	Description
J0217	Injection, velmanase alfa-tycv, 1 mg

Diagnosis Code	Description
E77.1	Defects in glycoprotein degradation

Loargys

HCPCS Code	Description
J1818	Injection, pegzilarginase-nbln, 0.05 mg

Diagnosis Code	Description
E27.21	Argininemia

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)

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Nexviazyme

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

Diagnosis Code	Description
E74.02	Pompe disease

Nulibry

HCPCS Code	Description
J1809	Injection, fosdenopterin, 0.1 mg

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

Pombiliti

HCPCS Code	Description
J1203	Injection, cipaglucosidase alfa-atga, 5 mg

Diagnosis Code	Description
E74.02	Pompe disease

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
J0218	Injection, olipudase alfa-rpcp, 1 mg

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

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sulfate. Aldurazyme therapy is to provide exogenous enzyme for uptake into lysosomes and increase the catabolism of GAG.

Avlayah (tividenofusp alfa-eknm) is a fusion protein consisting of the hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme iduronate-2-sulfatase (IDS) fused to the N-terminus of an immunoglobulin G1 (IgG1) fragment, crystallizable (Fc). Hunter syndrome is an inherited X-linked recessive lysosomal storage disease caused by a deficiency of iduronate-2-sulfatase (IDS), a lysosomal enzyme, that degrades heparan sulfate (HS) and dermatan sulfate (DS), the two primary GAGs in the lysosome. Insufficiency or absence of IDS leads to accumulation of GAGs, including HS and DS, and subsequent lysosome dysfunction in multiple organs and tissues, including the central nervous system (CNS). Avlayah provides an exogenous source of IDS. The fragment, crystallizable (Fc) component of tividenofusp alfa-eknm binds to the apical domain of the transferrin receptor (TfR) and delivers IDS to peripheral tissues and to the CNS through receptor-mediated transcytosis across the blood-brain barrier. Avlayah is internalized via binding to the mannose-6-phosphate receptor on the cell surface and transported into lysosomes where it is thought to exert enzymatic activity and reduce accumulated GAGs. In addition, since TfR is ubiquitously expressed, it is expected that the interaction of Avlayah and TfR will contribute to its uptake into cells in the brain and peripheral tissues.

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.

Elfabrio (pegunigalsidase alfa-iwxj) and **Fabrazyme** (agalsidase beta) are recombinant human α-galactosidase A enzymes. Fabry disease is caused by a deficiency of α-galactosidase A, a lyposomal enzyme that catalyzes the hydrolysis of globotriaosylceramide (GL-3) and other α-galactyl-terminated neutral glycosphingolipids, Elfabrio and Fabrazyme are intended to provide an exogenous source of α-galactosidase A and reduce accumulated Gb3 in Fabry disease patients.

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.

Lamzede (velmanase alfa-tycv) is recombinant human lysosomal alpha-mannosidase. Velmanase alfa-tycv is produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells. The amino acid sequence of the monomeric protein is identical to the naturally occurring human enzyme, alpha-mannosidase. Velmanase alfa-tycv has an approximate molecular weight of 130 kDa. Alpha-mannosidase catalyzes the degradation of accumulated mannose-containing oligosaccharides. The deficiency of alpha-mannosidase causes an intra-lysosomal accumulation of mannose-rich oligosaccharides in various tissues. Velmanase alfa-tycv provides an exogenous source of alphamannosidase. Velmanase alfa-tycv is internalized via binding to the mannose-6-phosphate receptor on the cell surface and transported into lysosomes where it is thought to exert enzyme activity.

Loargys (pegzilarginase-nbln) is a trimeric cobalt substituted recombinant human arginase 1 enzyme. Arginine 1 deficiency (ARG1-D) is an inherited metabolic disease characterized by deficiency of the arginase 1 enzyme and associated with the persistent elevation of plasma arginine. Loargys provides an exogenous source of the deficient human arginase 1 enzyme activity in patients with ARG1-D and reduces plasma arginine by converting it to urea and ornithine.

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.

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

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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.

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.

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.

Pombiliti (cipaglucosidase alfa-atga) is a hydrolytic lysosomal glycogen-specific recombinant human α-glucosidase (rhGAA) enzyme derived from a Chinese Hamster Ovary (CHO) cell line using perfusion methodology, resulting in cellularly (CHO)-derived N-glycans. Cipaglucosidase alfa-atga provides an exogenous source of GAA. The bis-M6P on cipaglucosidase alfa-atga mediates binding to M6P receptors on the cell surface with high affinity. After binding, it is internalized and transported into lysosomes where it undergoes proteolytic cleavage and N-glycans trimming which are both required to yield the most mature and active form of GAA. Cipaglucosidase alfa-atga then exerts enzymatic activity in cleaving glycogen. Miglustat binds with, stabilizes, and reduces inactivation of cipaglucosidase alfa-atga in the blood after infusion.

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

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.

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.

Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy.

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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. 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.

Avlayah

To confirm the efficacy and safety of Avlayah in patients with mucopolysaccharidosis II (MPS II), Muenzer et al. conducted a phase 1/2 multi-center, international, multi-cohort, single-arm, open-label trial of Avlayah in 47 pediatric patients with Hunter syndrome including 44 patients with neuronopathic Hunter syndrome and 3 patients with non-neuronopathic Hunter syndrome. Male participants up to 18 years of age with MPS II received weekly intravenous tividenofusp alfa for 24 weeks, followed by an 80-week safety extension and a 157-week open-label extension. The primary objective was to evaluate the safety of tividenofusp alfa. Secondary objectives were to evaluate central nervous system and peripheral effects as assessed by cerebrospinal fluid (CSF) and urinary heparan sulfate levels (HS), adaptive behavior (as assessed with the Vineland Adaptive Behavior Scales), and liver volume. Treatment with Avlayah resulted in a significant reduction of CSF HS. For the 44 patients who had measurements at Week 24, the CSF HS mean percent reduction from baseline was 91% (95% CI: 89%, 92%); the minimum and maximum percent change in CSF HS from baseline were 72% and 98%, respectively. At baseline, 0% (0 of 47) of patients had CSF HS levels below the upper limit of normal (ULN). At Week 24, 93% (41 of 44) of Avlayah-treated patients had CSF HS levels below the ULN. Avlayah is approved under accelerated approval based on reduction of cerebrospinal fluid heparan sulfate observed in patients treated with Avlayah. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial(s).

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 p = 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.

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Elfabrio

The efficacy of pegunigalsidase alfa-iwxj was first established in an open-label dose-ranging study in adults diagnosed with Fabry disease.[35-36] Patients received pegunigalsidase alfa-iwxj at 0.2 mg/kg, 1 mg/kg, or 2 mg/kg given intravenously every other week for 52 weeks. The 0.2 mg/kg and 2 mg/kg dosage regimens are not approved and are not recommended. The trial enrolled 18 patients who were ERT-naïve or who had not received ERT for more than 26 weeks and had a negative test for anti-pegunigalsidase alfa-iwxj IgG antibodies prior to enrollment. Two patients in the 1 mg/kg treatment group discontinued the trial after their first infusion; one of them discontinued due to severe hypersensitivity reaction. The average number of Gb3 inclusions per renal peritubular capillary in renal biopsy specimens of patients was assessed by light microscopy using the quantitative Barisoni Lipid Inclusion Scoring System (BLISS). Evaluable renal biopsies were obtained at baseline and at 26 weeks of treatment in 14 of the 16 patients. The mean change from baseline to 26 weeks in the BLISS score was -3.1 (95% CI: -4.8, -1.4).

Additionally, pegunigalsidase alfa-iwxj was evaluated in a randomized, double-blind, and active-controlled study in 77 ERT-experienced adults diagnosed with Fabry disease.[35,37] Eligible patients were treated with agalsidase beta for at least one year prior to trial entry (mean duration of agalsidase beta treatment prior to enrollment was 5.7 years). Patients were randomized to receive pegunigalsidase alfa-iwxj or agalsidase beta every 2 weeks for 104 weeks. A total of 77 patients were randomized and received at least one dose of pegunigalsidase alfa-iwxj (n = 52, 68%) or agalsidase beta (n = 25, 32%). The primary endpoint was the annualized rate of change in estimated glomerular filtration rate (eGFR slope) assessed over 104 weeks. The estimated mean eGFR slope was -2.4 and -2.3 mL/min/1.73 m^2/year on Elfabrio and Fabrazyme respectively. The estimated treatment difference was -0.1 (95% CI: -2.3, 2.1) mL/min/1.73 m^2/year. The most common adverse reactions (≥ 15%) reported with pegunigalsidase alfa-iwxj were infusion associated reactions which occurred in 17 patients (32%); followed by, nasopharyngitis and headache each in 11 patients (21%); diarrhea in 10 patients (19%); fatigue and nausea each in 9 patients (17%); and back pain, pain in extremity, and sinusitis each in 8 patients (15%). One pegunigalsidase alfa-iwxj-treated patient experienced a severe hypersensitivity reaction during the first infusion and withdrew from the trial following a moderate hypersensitivity reaction during the second infusion. And one case of membranoproliferative glomerulonephritis with immune depositions in the kidney was reported in a pegunigalsidase alfa-iwxj-treated patient.

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

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(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.

Lamzede

The efficacy of Lamzede was evaluated in a phase 3 multicenter, randomized, double-blinded, placebo-controlled, parallel group trial (rhLAMAN-05; NCT01681953) in adult and pediatric patients with alpha-mannosidosis. The trial evaluated the efficacy of Lamzede over 52 weeks at a dose of 1 mg/kg given weekly as an intravenous infusion. A total of 25 patients were enrolled (14 males, 11 females), including 13 adult patients (age range: ≥ 18 to 35 years; mean: 25 years) and 12 pediatric patients (age range: ≥ 6 to < 18 years; mean: 11 years); all patients were white. Ethnicity data were not collected. All patients had alphamannosidase activity below 11% of normal and in the range of 8 to 29 µmol/h/mg at baseline. All patients but one were naïve to Lamzede. Fifteen patients (8 adult and 7 pediatric) received Lamzede, and 10 patients (5 adult and 5 pediatric) received placebo. All patients completed the trial. The efficacy results for the clinical endpoints assessed at 12 months, 3-minute stair climbing test (3MSCT), 6-minute walking test (6MWT) and forced vital capacity (FVC) (% predicted), favored the Lamzede group and were supported by a reduction in serum oligosaccharide concentration. At week 52, the mean relative change in serum oligosaccharide concentration was significantly greater with Lamzede than with placebo (-77.6% versus -24.1%, respectively; adjusted mean difference, -70.5%; p < 0.001). At week 52, there was no significant change in the 3MSCT from baseline with Lamzede compared to placebo (mean change, -1.1% versus -0.0%, respectively; adjusted mean difference, + 3; p = 0.648). In addition, a small increase in the secondary endpoint of change from baseline in 6MWT at week 52 was seen in the Lamzede group compared with a small decline in the placebo group; the difference was not significant. Five serious TEAEs were reported, one of which was considered related to Lamzede in a patient who received long-term ibuprofen who experienced acute renal failure; the patient recovered after Lamzede interruption and was able to restart therapy without incident. The single-center, open-label, long-term (up to 4 years) phase 3 rhLAMAN-10 trial (NCT02478840) assessed Lamzede in 33 patients (14 adults, 19 pediatrics) with confirmed alpha-mannosidosis who had previously participated in phase 1/2 and phase 3 trials. The coprimary endpoint of serum oligosaccharide level was significantly reduced in the overall population at 12 months (mean change, -72.7%; p < 0.001) which was reported through the last observation timepoint (mean change, -62.8%; p < 0.001). An improvement in the other coprimary endpoint of change from baseline in 3MSCT was also observed at 12 months (mean change, + 9.3%; p = 0.013) and continued through the last observation (mean change, + 13.8%; p = 0.004).

Lamzede was also investigated in a single arm trial (NCT02998879) in pediatric alpha-mannosidosis patients less than 6 years of age. All patients had alpha-mannosidase activity below 10% of normal at baseline. The trial enrolled five patients ranging from 3.7 to 5.9 years of age, with a mean age of 4.5 years. Four patients were White, race was not recorded for 1 patient; and 3 were male and 2 were female. Patients received Lamzede 1 mg/kg as intravenous infusion once weekly (4 patients for 24 months, 1 patient for 40 months). The mean (SD) absolute and percentage changes from Baseline for serum oligosaccharides at 24 months were -7.7 (4.27) µmol/L and -65.8% (23.1%) respectively.

Loargys

The effectiveness of Loargys for the treatment of hyperargininemia in adult and pediatric patients with arginase-1 deficiency (ARG1-D) was evaluated in Trial 1 (NCT03921541). This study was a multicenter, double-blind, 24-week, placebo-controlled trial followed by a long-term open-label extension period of up to 150 weeks. A total of 32 patients were randomized in a 2:1 ratio to receive intravenous Loargys (n = 21) or placebo (n = 11) once weekly for 24 weeks. The primary endpoint in Trial 1 was the change from baseline in plasma arginine at Week 24. Patients treated with Loargys demonstrated a significant mean reduction in plasma arginine levels from baseline to Week 24. Additionally, 90% of Loargys-treated patients achieved target plasma arginine levels (below 200 µM) and normalized levels, compared with 0% of patients receiving placebo. All 31 patients (n = 20 Loargys; n = 11 placebo) who completed the double-blind period entered the extension phase and received open-label Loargys treatment. For the first eight weeks, patients previously treated with Loargys continued their weekly intravenous dosing, while those previously receiving placebo were initiated on weekly intravenous Loargys at 0.1 mg/kg. In both groups, the Loargys dose could be adjusted based on plasma arginine levels. After the first eight weeks, patients had the option to switch to weekly subcutaneous Loargys at the same dose as their intravenous regimen. Dosing could continue to be modified based on plasma arginine levels, up to a maximum of 0.2 mg/kg weekly. The median duration of Loargys exposure during the extension period–excluding the initial 24-week

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double-blind phase–was 94 weeks (range: 62 to 152 weeks). During the extension phase, patients who transitioned from placebo to Loargys achieved reductions in mean plasma arginine levels comparable to those observed in patients who had received Loargys from the start of the study. This indication is approved under accelerated approval based on reduction of plasma arginine. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

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's 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 -227 ±18 µg/mg more with rhASB than placebo (p < 0.001). 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

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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]

Pombiliti

The safety and efficacy of cipaglucosidase alfa-atga was evaluated in a randomized, double-blind, active-controlled, international, multi-center clinical trial (NCT#03729362) in patients ≥ 18 years old diagnosed with LOPD. Patients were randomized 2:1 to receive cipaglucosidase alfa-atga (20 mg/kg by intravenous infusion) in combination with miglustat (260 mg orally for those ≥ 50 kg or 195 mg orally for those ≥ 40 kg to < 50 kg) or a non-U.S.-approved alglucosidase alfa product with placebo every other week for 52 weeks. The efficacy population included a total of 123 patients of whom 95 (77%) had received prior treatment with U.S.-approved alglucosidase alfa or a non-U.S.-approved alglucosidase alfa product (ERT-experienced) and 28 (23%) were ERT-naïve. More than two thirds (n = 64, 67%) of ERT-experienced patients had been on ERT treatment for more than 5 years prior to entering Trial 1 (mean of 7.4 years). Key efficacy endpoints included assessment of sitting FVC (% predicted) and 6MWD.

Patients treated with cipaglucosidase alfa-atga in combination with miglustat showed a mean change in sitting FVC from baseline at Week 52 of -1.1% as compared with patients treated with a non-U.S.-approved alglucosidase alfa product with placebo of -3.3%; the estimated treatment difference was 2.3% (95% CI: 0.02, 4.62). The ERT-experienced patients treated with cipaglucosidase alfa-atga in combination with miglustat showed a numerically favorable change in sitting FVC from baseline at Week 52. Patients treated with cipaglucosidase alfa-atga in combination with miglustat walked on average 21 meters farther from baseline as compared to those treated with a non-U.S.-approved alglucosidase alfa product with placebo who walked 8 meters farther from baseline; the estimated treatment difference was 14 meters (95% CI: -1, 28). The ERT-experienced patients treated with cipaglucosidase alfa-atga in combination with miglustat showed a numerically favorable change in 6MWD from baseline at Week 52.

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 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

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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

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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.

Avlayah (tividenofusp alfa-eknm) is a hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme indicated for the treatment of neurologic manifestations of Hunter syndrome (Mucopolysaccharidosis type II, MPS II) when initiated in presymptomatic or symptomatic pediatric patients weighing at least 5 kg prior to advanced neurologic impairment.

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.

Elfabrio (pegunigalsidase alfa-iwxj) is indicated for the treatment of adults with confirmed with Fabry disease. Elfabrio reduces globotriaosylceramide (GL-3) accumulation in blood vessel walls of the kidneys, heart, and cerebrovascular system.

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.

Kanuma is indicated for the treatment of patients with a diagnosis of lysosomal Acid Lipase (LAL) deficiency.

Lamzede (velmanase alfa-tycv) is recombinant human lysosomal alpha-mannosidase indicated for the treatment of non-central nervous system manifestations of alpha-mannosidosis in adult and pediatric patients.

Loargys (pegzilarginase-nbln) is an arginine specific enzyme indicated for the treatment of hyperargininemia in adult and pediatric patients 2 years of age and older with Arginase 1 Deficiency (ARG1-D), in conjunction with dietary protein restriction.

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

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.

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.

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].

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

Pombiiliti (cipaglucosidase alfa-atga) is indicated, in combination with Opfolda (miglustat), an enzyme stabilizer, for the treatment of adult patients with late-onset Pompe disease [lysosomal acid alpha-glucosidase (GAA) deficiency] weighing ≥ 40 kg and who are not improving on their current enzyme replacement therapy (ERT).

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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).[1,5]

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]

Centers for Medicare and Medicaid Services (CMS)

Coverage guidelines for certain Part B drugs may be found in the Medicare Advantage Medical Policy titled Medications/Drugs (Outpatient/Part B). National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. These NCDs/LCDs/LCAs are available at https://www.cms.gov/medicare-coverage-database/new-search/search.aspx.

In general, Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that certain criteria are met, including that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals.

*Preferred therapy criteria does not apply to Medicare Advantage members.

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Policy History/Revision Information

Date	Summary of Changes
10/01/2026	**Coverage Rationale** • Removed reference link to the Medical Benefit Drug Policy titled *Review at Launch for New to Market Medications* for Loargys (pegzilarginase-nbln) and Avlayah (tividenofusp alfa-eknm) • Revised list of applicable medical therapies for enzyme deficiency products; added: ○ Avlayah™ (tividenofusp alfa-eknm) ○ Loargys® (pegzilarginase-nbln) • Added language to indicate: ○ Coverage for Avlayah and Loargys is contingent on criteria in the *Drug-Specific Criteria* section [of the policy] ○ **Avlayah (tividenofusp alfa)** is proven for the treatment of neurologic manifestations of Hunter syndrome (Mucopolysaccharidosis type II, MPS II); Avlayah is medically necessary when the following additional criteria are met: ***Initial Therapy*** ▪ Diagnosis of MPS II confirmed by one of 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 ▪ Presence of clinical signs and symptoms of the disease (e.g., hepatosplenomegaly, skeletal deformities, dysostosis, neurocognitive decline, cardiovascular disorders, etc.) ▪ Avlayah is not being used to treat MPS II in combination with Elaprase ▪ Dosing is in accordance with the FDA-approved labeling ▪ Initial authorization will be for no more than 12 months ***Continuation of Therapy*** ▪ Patient has previously received treatment with tividenofusp alfa ▪ Patient has experienced a positive clinical response to tividenofusp alfa therapy (e.g., improved hearing, improved functional capacity, improved neurological symptoms, reduced spleen volume, reduced urine glycosaminoglycan excretion, etc.) ▪ Avlayah is not being used to treat MPS II in combination with Elaprase ▪ Dosing is in accordance with the FDA-approved labeling ▪ Reauthorization will be for no more than 12 months ○ **Loargys (pegzilarginase)** is proven for the treatment of hyperargininemia; Loargys is medically necessary when the following additional criteria are met: ***Initial Therapy*** ▪ Diagnosis of hyperargininemia (arginase 1 deficiency) confirmed by one of the following: – Absence or deficiency of arginase 1 enzyme activity – Genetic variants in the ARG1 gene ▪ Presence of clinical signs and symptoms of the disease (e.g., loss of motor skills, intellectual disability, developmental delay) ▪ Dosing is in accordance with the FDA-approved labeling ▪ Initial authorization will be for no more than 12 months ***Continuation of Therapy*** ▪ Patient has previously received treatment with pegzilarginase therapy ▪ Patient has experienced a positive clinical response to pegzilarginase therapy (e.g., improved motor function, improved pulmonary function) ▪ Dosing is in accordance with the FDA-approved labeling ▪ Reauthorization will be for no more than 12 months • Revised coverage criteria for Elaprase (idursulfase) for the treatment of mucopolysaccharidosis II (MPS II, Hunter syndrome); added criterion requiring Elaprase is not being used to treat MPS II in combination with Avlayah **Applicable Codes** ***Avlayah*** • Added HCPCS code J1757

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Date	Summary of Changes
	• Added ICD-10 diagnosis code E76.1 ***Loargys*** • Added HCPCS code J1818 • Added ICD-10 diagnosis code E27.21 **Supporting Information** • Updated *Background*, *Clinical Evidence*, *FDA*, and *References* sections to reflect the most current information • Archived previous policy version 2026D0052AE

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, check the member specific benefit plan document and any applicab6le federal or state mandates. UnitedHealthcare reserves the right to modify its policies and guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

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