LifeWise
Health Plan of Washington

PHARMACY / MEDICAL POLICY – 5.01.576

Drugs for Rare Diseases

BCBSA Ref. Policy: 5.01.37 and 5.01.40

Effective Date:	Sep. 1, 2026	RELATED PHARMACY / MEDICAL POLICIES:
Last Revised:	Aug. 11, 2026	11.01.523 Site of Service: Infusion Drugs and Biologic Agents
Replaces:	N/A	

The Site of Service Medical Necessity criteria within this policy DO NOT apply to Alaska fully-insured members; refer to the infusion and injection drug Medical Necessity criteria only.

Site of Service *and* the infusion and injection drug Medical Necessity criteria apply to all other plan members.

Please contact Customer Service for more information.

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | APPENDIX | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Lysosome storage diseases (LSD) are a group of rare inherited metabolic disorders that result from defects in lysosomal function. Lysosomes digest large molecules and pass them along to the other parts of the cell for recycling. Deficiency of critical lysosomal enzymes can lead to accumulation of partially degraded glycosaminoglycan (GAGs) which results in disruption of cellular function and, sometimes, failure of active transport of small molecules from lysosomes. The primary treatment for LSD is enzyme replacement therapy (ERT). In addition to LSD, there are a number of other inherited rare diseases that happen when a critical enzyme or other protein either can't be made by the body or is doesn't work properly. Treatments for these are very specific, and a genetic test is usually needed to decide whether the treatment will work for a particular person. In other cases, the person may produce too much of a substance, and the drug targets this imbalance.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Site of Service (SOS) Medical Necessity criteria applies ONLY to medical benefit reviews. SOS Medical Necessity criteria does NOT apply to Alaska fully-insured members; refer to the infusion and injection drug Medical Necessity criteria only. Please contact Customer Service for more information.

We will review specific intravenous (IV) and injectable drugs for medical necessity for all ages.

For those aged 13 and older, we also will review the site of service for medical necessity. Site of service is defined as the location where the drug is administered, such as a hospital-based outpatient setting, an infusion center, a physician's office, or at home. Click **here** to be directed to the site of service review criteria.

Drugs subject to site of service review addressed in this policy are:

- Aldurazyme (laronidase)
- Cerezyme (imiglucerase)
- Crysvita (burosumab)
- Elaprase (idursulfase)
- Elelyso (taliglucerase alfa)
- Fabrazyme (agalsidase beta)
- Givlaari (givosiran)
- Kanuma (sebelipase alfa)
- Lumizyme (alglucosidase alfa)
- Mepsevii (vestronidase alfa-vjbk)
- Naglazyme (galsulfase)
- Nexviazyme (avalglucosidase alfa-ngpt)
- Tepezza (teprotumumab-trbw)
- Vimizim (elosulfase alfa)
- Vpriv (velaglucerase alfa)

Click on the links below to be directed to the related medical necessity criteria:

Achondroplasia

Acid Sphingomyelinase Deficiency (ASMD)

Acquired Thrombotic Thrombocytopenic Purpura (aTTP)

Adenosine Deaminase Severe Combined Immune Deficiency

Alagille Syndrome

Alpha-Mannosidosis

Alpha- or Beta-Thalassemia

Barth Syndrome

Cerebrotendinous Xanthomatosis (CTX)

Congenital Adrenal Hyperplasia (CAH)

Neuronal Ceroid Lipofuscinoses (NCLs)

Niemann-Pick Disease Type C (NPC)

Periodic Paralysis

Plasminogen Deficiency (PLGD) Type I

Polycythemia Vera

POMC, PCSK1, or LEPR Deficiency

Pompe Disease

Primary Hyperoxaluria Type 1 (PH1)

Progeroid Syndromes

Proliferating Infantile Hemangioma

Bile Acid Synthesis Disorders

Castleman's Disease

Cold Agglutinin Disease (CAD)

Fabry Disease

Fibrodysplasia Ossificans Progressiva

Friedreich's Ataxia

Gaucher's Types 1 Disease

Hemophagocytic Lymphohistiocytosis

Hepatic Porphyria

Hereditary Orotic Aciduria

Homocystinuria

Hypoparathyroidism

Lambert-Eaton Myasthenic Syndrome

Long-Chain Fatty Acid Oxidation Disorders (LC-FAOD)

Lysosomal Acid Lipase Deficiency

Menkes Disease

Molybdenum Cofactor Deficiency (MoCD) Type A

Mucopolysaccharidosis Type I

Mucopolysaccharidosis Type II

Mucopolysaccharidosis Type IVA

Mucopolysaccharidosis Type VI

Mucopolysaccharidosis Type VII

Paroxysmal Nocturnal Hemoglubinuria

Prader-Willi Syndrome (PWS)

Progressive Familial Intrahepatic Cholestasis

Pyruvate Kinase (PK) Deficiency

Rett Syndrome

Short Bowel Syndrome

Site of Service

Sucrase Deficiency

Site of Service Administration	Medical Necessity
Medically necessary sites of service • **Physician's office** • **Infusion center** • **Home infusion**	**IV infusion and injection therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site:** • These are the preferred **medically necessary** sites of service for specified drugs.
Hospital-based outpatient setting • **Outpatient hospital IV infusion department** • **Hospital-based outpatient clinical level of care**	**IV infusion and injection therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site.** **This site is considered medically necessary for the first 90 days for the following:** • The initial course of infusion or injection of a pharmacologic or biologic agent **OR** • Re-initiation of an agent after 6 months or longer following discontinuation of therapy* **Note:** *This does not include when standard dosing between infusions or injections is 6 months or longer **This site is considered medically necessary when there is no outpatient infusion center within 50 miles of the individual's home and there is no contracted home infusion agency that will travel to their home, or a hospital is the only place that offers infusions or injections of this drug.** **This site is considered medically necessary only when the individual has a clinical condition which puts him or her at increased risk of complications for infusions or injections, including any 1 of the following:**

Site of Service Administration	Medical Necessity

	• Known cardiac condition (e.g., symptomatic cardiac arrhythmia) or pulmonary condition (e.g., significant respiratory disease, serious obstructive airway disease, FVC less than or equal to 40%) that may increase the risk of an adverse reaction
	• Unstable renal function which decreases the ability to respond to fluids
	• Difficult or unstable vascular access
	• Acute mental status changes or cognitive conditions that impact the safety of infusion or injection therapy
	• A known history of severe adverse drug reactions and/or anaphylaxis to prior treatment with a related or similar drug
	
	This site is considered medically necessary when the individual has cytokine release syndrome (CRS) and all the following are met:
	• CRS is grade 3 or 4 as evidenced by ALL the following:
	  ○ Temperature at least 38 °C
	  ○ Hypotension that requires 1 or more vasopressors
	  ○ Hypoxia that requires oxygen through a high-flow nasal cannula, face mask, non-rebreather mask, or Venturi mask OR positive pressure (continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP], intubation, or mechanical ventilation)
	AND
	• The individual will be admitted into an inpatient setting as soon as possible

Hospital-based outpatient setting • **Outpatient hospital IV infusion department** • **Hospital-based outpatient clinical level of care**	**These sites are considered not medically necessary for infusion and injectable therapy services of various medical and biologic agents when the site-of-service criteria in this policy are not met.**

Drug	Medical Necessity
Fabry Disease	
First-line: • **Elfabrio (pegunigalsidase alfa-iwxj) IV**	**Elfabrio (pegunigalsidase alfa-iwxj) may be considered medically necessary when the following are met:** • The individual is aged 18 years or older **AND** • Has been diagnosed with Fabry disease **AND** • Elfabrio (pegunigalsidase alfa-iwxj) is not used in combination with Galafold (migalastat) and Fabrazyme (agalsidase beta) **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.
First-line: • **Fabrazyme (agalsidase beta) IV**	**Fabrazyme (agalsidase beta) IV is subject to review for site of service administration.** **Fabrazyme (agalsidase beta) may be considered medically necessary when the following are met:** • The individual is aged 2 years or older **AND** • Has been diagnosed with Fabry disease **AND** • Fabrazyme (agalsidase beta) is not used in combination with Galafold (migalastat) and Elfabrio (pegunigalsidase alfa-iwxj) **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.

Drug	Medical Necessity
First-line: • **Galafold (migalastat) oral**	**Galafold (migalastat) may be considered medically necessary in individuals with Fabry disease who meet the following criteria:** • The individual is aged 16 years or older **AND** • Has documented evidence of Fabry disease with appropriate genotyping completed **AND** • A confirmed amenable *galactosidase A* enzyme mutation as provided in the **package insert** **AND** • Recent laboratory tests confirming GFR greater than 30 mL/min/1.73 m^2 **AND** • Galafold (migalastat) is not used in combination with Fabrazyme (agalsidase beta) and Elfabrio (pegunigalsidase alfa-iwxj) **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.
Pompe Disease	
First-line: • **Lumizyme (alglucosidase alfa) IV**	**Lumizyme (alglucosidase alfa) IV is subject to review for site of service administration.** **Lumizyme (alglucosidase alfa) may be considered medically necessary when the following are met:** • The individual must be diagnosed with Pompe disease (acid α-glucosidase [GAA] deficiency) as confirmed by 1 of the following: ○ Documented GAA enzyme deficiency **OR**

Drug	Medical Necessity
	○ Genetic testing documenting at least 1 mutation in the GAA gene **AND** • Lumizyme (alglucosidase alfa) is not used concurrently with Nexviazyme (avalglucosidase alfa-ngpt) **AND** • The dose prescribed is no more than 20 mg per kg body weight administered every 2 weeks **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.
First-line: • **Nexviazyme (avalglucosidase alfa-ngpt) IV**	**Nexviazyme (avalglucosidase alfa-ngpt) IV is subject to review for site of service administration.** **Nexviazyme (avalglucosidase alfa-ngpt) may be considered medically necessary for the treatment of late-onset Pompe disease when the following criteria are met:** • The individual is aged 1 years or older **AND** • Diagnosed with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency) as confirmed by 1 of the following: ○ Documented GAA enzyme deficiency **OR** ○ Genetic testing documenting at least 1 mutation in the GAA gene **AND** • Baseline documentation is provided for the forced expiratory volume in one second (FEV1) and the value is between at least 30% and at most 85% predicted ○ **Exception:** For individuals less than 5 years of age there is no requirement to receive a documented FEV1 value **AND**

Drug	Medical Necessity

	• Baseline documentation is provided and the individual is able to ambulate (with or without assistance*) and complete a 6-minute walk test (6MWT) of at least 40 meters
	  ○ **Exception:** For individuals less than 5 years of age there is no requirement to receive a 6MWT value
	AND
	• Nexviazyme (avalglucosidase alfa-ngpt) is not used concurrently with Lumizyme (alglucosidase alfa)
	AND
	• The maximum dose prescribed is:
	  ○ 40 mg/kg every 2 weeks for actual body weight less than 30 kg
	  ○ 20 mg/kg every 2 weeks for actual body weight 30 kg or greater
	
	Initial therapy may be approved up to 12 months.
	
	Re-authorization criteria:
	• Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response and is tolerating therapy. For individuals at least 5 years of age documentation of stability or improvement in the FEV1 and/or 6MWT is required.
	
	*Assistance not to include use of a wheelchair

First-line: • **Pombiliti (cipaglucosidase alfa-atga) IV and Opfolda (miglustat) oral**	**Pombiliti (cipaglucosidase-alfa-atga) and Opfolda (miglustat) may be considered medically necessary for the treatment of late-onset Pompe disease when the following criteria are met:** • The individual is aged 18 years or older **AND** • Weighs at least 40 kg **AND** • Diagnosed with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency) as confirmed by 1 of the following: ○ Documented GAA enzyme deficiency

Drug	Medical Necessity
	OR ○ Genetic testing documenting at least 1 mutation in the GAA gene **AND** • Baseline documentation is provided for the forced expiratory volume in one second (FEV1) and the value is between 30% and 85% predicted despite current treatment with an enzyme replacement therapy (ERT) such as Nexviazyme (avalglucosidase alfa-ngpt) or Lumizyme (alglucosidase alfa) **AND** • Baseline documentation is provided and individual is not able to ambulate (with or without assistance*) and complete a 6-minute walk test (6MWT) of at least 75 meters despite current treatment with an enzyme replacement therapy (ERT) such as Nexviazyme (avalglucosidase alfa-ngpt) or Lumizyme (alglucosidase alfa) **AND** • Pombiliti (cipaglucosidase alfa-atga) and Opfolda (miglustat) will be used concurrently **AND** • Pombiliti (cipaglucosidase alfa-atga) and Opfolda (miglustat) are not used concurrently Nexviazyme (avalglucosidase alfa-ngpt) or Lumizyme (alglucosidase alfa) **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response with documentation of stability or improvement in FEV1 and/or 6MWT and is tolerating therapy ***** Assistance not to include use of a wheelchair **Note:** See the **Niemann-Pick type C (NPC) disease section** for the NPC medical necessity criteria

Drug	Medical Necessity
Gaucher's Types 1 Disease	

First-line:
• **Cerdelga (eliglustat) oral**
	Cerdelga (eliglustat) may be considered medically necessary when the following criteria are met:
	• The individual is aged 16 years or older
	AND
	• Diagnosed with Type I Gaucher's disease as confirmed by genetic testing that documents a mutation in the glucocerebrosidase enzyme
	AND
	• Must have 1 or more of following conditions:
	  ○ Anemia
	  ○ Thrombocytopenia
	  ○ Bone disease
	  ○ Hepatomegaly
	  ○ Splenomegaly
	
	Initial therapy may be approved up to 12 months.
	
	Re-authorization criteria:
	• Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy as documented by an improved or sustained response to one of the following:
	  ○ Hemoglobin concentrations are normal to near-normal levels
	  ○ Platelet counts return to normal or near-normal levels
	  ○ Reduction in spleen and liver volumes
	  ○ Improvement in bone structure
	  ○ Reduction in individual fatigue as measured by a validated fatigue scoring system

First-line: • **Cerezyme (imiglucerase) IV**	**Cerezyme (imiglucerase) IV is subject to review for site of service administration.** **Cerezyme (imiglucerase) may be considered medically necessary when the following criteria are met:**

Drug	Medical Necessity

	• The individual is diagnosed with Type I or Type 3 Gaucher's disease as confirmed by genetic testing that documents a mutation in the glucocerebrosidase enzyme
	AND
	• Must have 1 or more of following conditions:
	  ○ Anemia
	  ○ Thrombocytopenia
	  ○ Bone disease
	  ○ Hepatomegaly
	  ○ Splenomegaly
	
	Initial therapy may be approved up to 12 months.
	
	Re-authorization criteria:
	• Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy as documented by an improved or sustained response to one of the following:
	  ○ Hemoglobin concentrations are normal to near-normal levels
	  ○ Platelet counts return to normal or near-normal levels
	  ○ Reduction in spleen and liver volumes
	  ○ Improvement in bone structure
	  ○ Reduction in individual fatigue as measured by a validated fatigue scoring system

First-line: • **Elelyso (taliglucerase alfa) IV**	**Elelyso (taliglucerase alfa) IV is subject to review for site of service administration.** **Elelyso (taliglucerase alfa) may be considered medically necessary when the following criteria are met:** • The individual is aged 4 years or older **AND** • Diagnosed with Type I Gaucher's disease as confirmed by genetic testing that documents a mutation in the glucocerebrosidase enzyme

Drug	Medical Necessity

	Initial therapy may be approved up to 12 months.
	
	Re-authorization criteria:
	• Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy as documented by an improved or sustained response to one of the following:
	  ○ Hemoglobin concentrations are normal to near-normal levels
	  ○ Platelet counts return to normal or near-normal levels
	  ○ Reduction in spleen and liver volumes
	  ○ Improvement in bone structure
	  ○ Reduction in individual fatigue as measured by a validated fatigue scoring system

First-line: • **Generic miglustat oral** • **Yargesa (generic miglustat) oral**	**Generic miglustat and Yargesa (generic miglustat) may be considered medically necessary when the following are met:** • The individual is aged 18 years or older **AND** • Diagnosed with Type I Gaucher's disease as confirmed by genetic testing that documents a mutation in the glucocerebrosidase enzyme **AND** • Medication is prescribed by or in consultation with a geneticist, endocrinologist, metabolic disorder sub-specialist, hematologist, or a physician who specializes in the treatment of Gaucher Disease. **AND** • Enzyme replacement therapy is not a therapeutic option for the individual (e.g., due to constraints such as allergy, hypersensitivity, or poor venous access) **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes

Drug	Medical Necessity
	demonstrate that the individual continues to show a positive clinical response to therapy. **Note:** See the **Neimann-Pick disease type C (NPC) section** for the NPC medical necessity criteria
First-line: • **Vpriv (velaglucerase alfa) IV**	**Vpriv (velaglucerase alfa) IV is subject to review for site of service administration.** **Vpriv (velaglucerase alfa) may be considered medically necessary when the following criteria are met:** • The individual is aged 4 years or older **AND** • Diagnosed with Type I Gaucher's disease as confirmed by genetic testing that documents a mutation in the glucocerebrosidase enzyme **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy as documented by an improved or sustained response to one of the following: o Hemoglobin concentrations are normal to near-normal levels o Platelet counts return to normal or near-normal levels o Reduction in spleen and liver volumes o Improvement in bone structure o Reduction in individual fatigue as measured by a validated fatigue scoring system
Second-line: • **Zavesca (miglustat) oral**	**Zavesca (miglustat) may be considered medically necessary when the following criteria are met:** • The individual is aged 18 years or older **AND**

Drug	Medical Necessity
	• Diagnosed with Type I Gaucher's disease as confirmed by genetic testing that documents a mutation in the glucocerebrosidase enzyme **AND** • Zavesca (miglustat) is prescribed by or in consultation with a geneticist, endocrinologist, metabolic disorder sub-specialist, hematologist, or a physician who specializes in the treatment of Gaucher Disease. **AND** • Enzyme replacement therapy is not a therapeutic option for the individual (e.g., due to constraints such as allergy, hypersensitivity, or poor venous access) **AND** • Medical records indicate that the individual has tried and failed BOTH of the following preferred products: ○ Cerdelga (eliglustat capsules) **AND** ○ Generic miglustat **AND** • Brand Zavesca is being requested due to a formulation difference in the inactive ingredient(s) [e.g., preservatives] between the brand and the bioequivalent generic product, which, per the prescribing physician has or would result in a significant allergy or serious adverse reaction. **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy. **Note:** See the **Niemann Pick disease type C (NPC) section** for the NPC medical necessity criteria
Hereditary Orotic Aciduria	

Drug	Medical Necessity
Xuriden (uridine triacetate) oral	**Xuriden (uridine triacetate) may be considered medically necessary when the following criteria are met:** • The individual is diagnosed with hereditary orotic aciduria **AND** • Laboratory tests document significantly elevated levels of urinary orotic acid at time of diagnosis **AND** • The max dose of Xuriden does not exceed 8 grams once daily **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.
Homocystinuria	

Generic betaine anhydrous oral	**Generic betaine anhydrous may be considered medically necessary when the following criteria are met:**
	• The individual has a confirmed diagnosis of homocystinuria based on genetic testing demonstrating 1 of the following:
	  ○ Cystathionine beta-synthase deficiency
	  ○ 5,10-methylenetetrahydrofolate reductase deficiency
	  ○ Cobalamin cofactor metabolism defect
	AND
	• Has tried or is concurrently receiving vitamin B6 (pyridoxine), vitamin B12 (cobalamin), or folate supplementation
	
	Initial approval may be approved up to 12 months.
	
	Re-authorization criteria:
	• Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.

Drug	Medical Necessity

Cystadane (betaine anhydrous) oral	**Cystadane (betaine anhydrous) may be considered medically necessary when the following criteria are met:**
	• The individual has a confirmed diagnosis of homocystinuria based on genetic testing demonstrating 1 of the following:
	  ○ Cystathionine beta-synthase deficiency
	  ○ 5,10-methylenetetrahydrofolate reductase deficiency
	  ○ Cobalamin cofactor metabolism defect
	AND
	• Has tried or is concurrently receiving vitamin B6 (pyridoxine), vitamin B12 (cobalamin), or folate supplementation
	AND
	• Has tried generic betaine anhydrous and had an inadequate response or intolerance
	
	Initial therapy may be approved up to 12 months.
	
	Re-authorization criteria:
	• Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.

Hypoparathyroidism	
Yorvipath (palopegteriparatide) SC	**Yorvipath (palopegteriparatide) may be considered medically necessary for the treatment of hypoparathyroidism when all the following criteria are met:** • The individual is aged 18 years or older **AND** • Has a confirmed diagnosis of hypoparathyroidism based on hypocalcemia and low serum PTH levels for at least 26 weeks **AND** • Has tried or is concurrently receiving calcium and vitamin D **AND** • Has a serum 25 (OH) vitamin D in normal range **AND** • Has an albumin-adjusted serum calcium of at least 7.8 mg/dL **AND**

Drug	Medical Necessity
	• Yorvipath (palopegteriparatide) is prescribed by or in consultation with an endocrinologist **AND** • The dose is limited to 30 mcg daily **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met, chart notes demonstrate that the individual continues to show a positive clinical response to therapy, and a recent albumin-adjusted serum calcium is at least 7.8 mg/dL
Mucopolysaccharidosis Type I (MPS I)	

Aldurazyme (laronidase) IV	**Aldurazyme (laronidase) IV is subject to review for site of service administration.**
	
	Aldurazyme (laronidase) may be considered medically necessary when the following criteria are met:
	• The individual is aged 6 months or older
	AND
	• Diagnosed with mucopolysaccharidosis type I (MPS I; Includes Hurler, Hurler-Scheie, and Scheie forms) as confirmed by 1 of the following:
	  ○ Documented alpha-L-iduronidase enzyme deficiency
	  ○ Genetic testing documenting mutations in the IDUA gene encoding alpha-L-iduronidase
	
	Initial therapy may be approved up to 12 months.
	
	Re-authorization criteria:
	• Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.

Mucopolysaccharidosis Type II (MPS II)	

Drug	Medical Necessity
Elaprase (idursulfase) IV	**Elaprase (idursulfase) IV is subject to review for site of service administration.** **Elaprase (idursulfase) may be considered medically necessary when the following criteria are met:** • The individual is aged 5 years or older **AND** • Diagnosed with Hunter syndrome (mucopolysaccharidosis II; MPS II) **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.
X-Linked Hypophosphatemia	
Crysvita (burosumab) SC	**Crysvita (burosumab) SC is subject to review for site of service administration.** **Crysvita (burosumab) may be considered medically necessary when the following criteria are met:** • The individual is aged 6 months or older **AND** • Diagnosed with X-linked hypophosphatemia (XLH), as documented by radiographic evidence of rickets or osteomalacia **AND** • Genetic test confirming presence of a PHEX (Phosphate regulating Endopeptidase on the X chromosome) mutation **Crysvita (burosumab) may be considered medically necessary for the treatment of fibroblast growth factor 23 (FGF23)-related hypophosphatemia in tumor induced osteomalacia**

Drug	Medical Necessity
	(TIO) associated with phosphaturic mesenchymal tumors when the following criteria are met: • The individual is aged 2 years or older **AND** • The tumor cannot be curatively resected or localized **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.
Mucopolysaccharidosis Type IVA (MPS IVA)	
Vimizim (elosulfase alfa) IV	**Vimizim (elosulfase alfa) IV is subject to review for site of service administration.** **Vimizim (elosulfase alfa) may be considered medically necessary when the following criteria are met:** • The individual is aged 5 years or older **AND** • Diagnosed with mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome) **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.
Mucopolysaccharidosis Type VI (MPS VI)	
Naglazyme (galsulfase) IV	**Naglazyme (galsulfase) IV is subject to review for site of service administration.**

Drug	Medical Necessity
	Naglazyme (galsulfase) may be considered medically necessary when the following criteria are met: • The individual is aged 3 months or older **AND** • Diagnosed with mucopolysaccharidosis type VI (MPS VI; Maroteaux-Lamy syndrome) as confirmed by one of the following: ○ Documented arylsulfatase B (ARSB, N-acetylgalactosamine 4-sulfatase) enzyme deficiency **OR** ○ Genetic testing documenting mutations in the gene encoding arylsulfatase B (ARSB, N-acetylgalactosamine 4-sulfatase) **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.
Mucopolysaccharidosis Type VII (MPS VII)	
Mepsevii (vestronidase alfa-vjbk) IV	**Mepsevii (vestronidase alfa-vjbk) IV is subject to review for site of service administration.** **Mepsevii (vestronidase alfa-vjbk) may be considered medically necessary in pediatric and adult individuals when the following criteria are met:** • Diagnosed with mucopolysaccharidosis type VII (MPS VII; Sly syndrome) as confirmed by 1 of the following: ○ Documented beta-glucuronidase enzyme deficiency **OR** ○ Genetic testing documenting mutations in the gene encoding beta-glucuronidase (GUSB gene) **Initial therapy may be approved up to 12 months.**

Drug	Medical Necessity
	Re-authorization criteria: • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.
Adenosine Deaminase Severe Combined Immune Deficiency (ADA-SCID)	
Revcovi (elapegademase-lvlr) IM	**Revcovi (elapegademase-lvlr) may be considered medically necessary when the following criteria are met:** • The individual must be diagnosed with adenosine deaminase severe combined immune deficiency (ADA-SCID) **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.
Lambert-Eaton Myasthenic Syndrome (LEMS)	
Firdapse (amifampridine) oral	**Firdapse (amifampridine) may be considered medically necessary when the following criteria are met:** • The individual must be diagnosed with Lambert-Eaton myasthenic syndrome (LEMS) **AND** • The diagnosis is supported by documentation from: ○ Electrodiagnostic study **OR** ○ Voltage-gated calcium channels antibody testing **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes

Drug	Medical Necessity
	demonstrate that the individual continues to show a positive clinical response to therapy.
Long-Chain Fatty Acid Oxidation Disorders (LC-FAOD)	
Dojolvi (triheptanoin) oral	**Dojolvi (triheptanoin) may be considered medically necessary when the following criteria are met:** • The individual must be diagnosed with molecularly confirmed long-chain fatty acid oxidation disorders (LC-FAOD) **AND** • Tried and failed or had intolerance to over-the-counter medium-chain triglyceride (MCT) oil unless contraindicated **AND** • Has elevated mean creatine kinase (CK) levels greater than 2X the upper limit of normal matched by age and gender OR greater than 500 units/L (see Appendix) **AND** • For individuals 7 years of age or older, documentation of at least 4 emergency department or hospitalization events related to disease severity in the last two years **AND** • Provider attestation the individual is on a low-fat/high-carbohydrate diet **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.
Acquired Thrombotic Thrombocytopenic Purpura (aTTP)	
Cablivi (caplacizumab-yhdp) IV/SC	**Cablivi (caplacizumab-yhdp) may be considered medically necessary when the following criteria are met:** • The individual is aged 12 years or older **AND** • Diagnosed with acquired thrombotic thrombocytopenic purpura (aTTP)

Drug	Medical Necessity
	AND • Cablivi (caplacizumab-yhdp) is used in combination with plasma exchange and immunosuppressive therapy **Initial therapy may be approved up to 90 days.** **Re-authorization criteria:** • Future re-authorization of continuous use of Cablivi (caplacizumab-yhdp) beyond 90 days is considered investigational. A future episode of aTTP will be reviewed as an initial request.
Thalassemia	

Aqvesme (mitapivat) oral	**Aqvesme (mitapivat) may be considered medically necessary when the following criteria are met:**
	• The individual is aged 18 years or older
	AND
	• Has a diagnosis of alpha- or beta-thalassemia
	AND
	• Meets 1 of the following:
	  ○ Is transfusion-dependent requiring 6 to 20 RBC units transfused and no longer than a 6-week transfusion-free period
	  ○ Is non-transfusion-dependent and has a baseline hemoglobin less than or equal to 10 g/dL
	AND
	• Is not being used as a substitute for RBC transfusions in individuals who require immediate correction of anemia
	AND
	• Does not have cirrhosis (Child-Pugh Class A, B, or C)
	AND
	• Liver tests (ALT, AST, alkaline phosphatase, total bilirubin) will be monitored according to the requirements of the REMS program
	AND
	• Does not have prior exposure to gene therapy or prior bone marrow or stem cell transplantation

Drug	Medical Necessity
	AND • Medication is prescribed by or in consultation with a hematologist **AND** • Aqvesme (mitapivat) will not be used in combination with Reblozyl (luspatercept-aamt) **AND** • The dose is limited to 100 mg twice daily (56 tablet per 28 days) **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the above conditions are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy as documented by improvement in anemia and/or transfusion burden from baseline.
Thymidine Kinase 2 Deficiency	
Kygevvi (doxecitine and doxribtimine) oral	**Kygevvi (doxecitine and doxribtimine) may be considered medically necessary when the following criteria are met:** • The individual has a diagnosis of thymidine kinase 2 deficiency (TK2d) confirmed by genetic testing that detects variants in TK2 gene **AND** • Documentation of initial symptoms onset at age 12 years or younger consistent with childhood onset of TK2d (e.g., hypotonia, limb weakness, feeding or breathing difficulties, developmental delay, ptosis, and/or progressive external ophthalmoparesis) **AND** • Does not have other genetic disease, polygenic disease, or inborn errors of metabolism **AND** • Prescribed by or in consultation with a neurologist

Drug	Medical Necessity
	AND • The dose is limited to 800 mg/kg per day **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.
Thyroid Eye Disease	

Tepezza (teprotumumab-trbw) IV	**Tepezza (teprotumumab-trbw) is subject to review for site of service administration.**
	
	Tepezza (teprotumumab-trbw) may be considered medically necessary when the following criteria are met:
	• The individual is aged 18 years or older
	AND
	• Diagnosed with Grave's disease with active moderate or severe thyroid eye disease as documented by 1 or more of the following:
	  ○ Lid retraction of at least 2 mm
	  ○ Moderate or severe soft-tissue involvement
	  ○ Proptosis at least 3 mm above normal values for race and sex
	  ○ Transient or constant diplopia
	AND
	• Has tried glucocorticoids and had an inadequate response or intolerance to glucocorticoids
	AND
	• Tepezza is administered within 9 months of completing the glucocorticoid trial
	AND
	• Documentation of 1 of the following:

Drug	Medical Necessity
	○ A euthyroid state as documented by thyroid function tests showing a normal free thyroxine (T4) and normal free triiodothyronine (T3) levels **OR** ○ Thyroid function tests show a free T4 and free T3 levels less than 50% above or below normal limits as defined by laboratory standard **AND** • Documented Clinical Activity Score (CAS) is at least 4 **AND** • For individuals of reproductive potential, attestation that the individual is NOT pregnant and has been informed that appropriate forms of contraception should be implemented prior to initiation, during treatment and for 6 months following the last dose of Tepezza **AND** • Prescribed by or in consultation with an ophthalmologist or endocrinologist **AND** • Tepezza is not being used in combination with another biologic immunomodulator (e.g., rituximab, tocilizumab) for the treatment of TED **Initial therapy may be approved up to 24 weeks. The limit is 8 courses (3 weeks for each course) of treatment.** **Re-authorization criteria:** • Future re-authorization of Tepezza (teprotumumab-trbw) beyond six months is considered investigational.
Hepatic Porphyria	
Givlaari (givosiran) SC	**Givlaari (givosiran) SC is subject to review for site of service administration.** **Givlaari (givosiran) may be considered medically necessary when the following criteria are met:** • The individual is aged 18 years or older

Drug	Medical Necessity

	AND
	• Diagnosed with acute hepatic porphyria (AHP)
	AND
	• Laboratory tests document elevated urinary or plasma levels greater than the upper limit of normal at time of diagnosis for 1 or both of the following:
	  ○ Porphobilinogen (PBG)
	  ○ Aminolaevulinic acid (ALA)
	AND
	• Genetic testing confirms a mutation in at least 1 of the following genes:
	  ○ ALAD (gamma-aminolaevulinic acid dehydratase)
	  ○ CPOX (coproporphyrinogen oxidase)
	  ○ HMBS (hydroxymethylbilane synthase)
	  ○ PPOX (protoporphyrinogen oxidase)
	AND
	• Active disease has been documented with at least one porphyria attacks requiring hospitalization, urgent healthcare visit, or intravenous hemin administration, within the past year
	AND
	• Givlaari is prescribed by a hematologist, hepatologist, gastroenterologist, dermatologist, or neurologist
	
	Initial therapy may be approved up to 12 months.
	
	Re-authorization criteria:
	• Continued therapy may be approved up to 12 months as long as the above conditions are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy as documented by:
	  ○ Improvement in symptoms
	  AND
	  ○ Reduced number of porphyria attacks requiring hospitalization, urgent healthcare visit, or intravenous hemin administration from baseline
	  AND

Drug	Medical Necessity
	○ Urinary or plasma ALA OR PBG levels has not increased from baseline
Short Bowel Syndrome	
Gattex (teduglutide) SC	**Gattex (teduglutide) may be considered medically necessary when the following criteria are met:** • The individual is aged 1 year or older **AND** • Has a diagnosis of short bowel syndrome (SBS) **AND** • Is dependent on parenteral nutrition support **AND** • Gattex is prescribed by or in consultation with a gastroenterologist **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the above conditions are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy as documented by at least 20% reduction in weekly parenteral nutrition IV volume from baseline (prior to initiation of therapy).
Periodic Paralysis	
Keveyis (dichlorphenamide) oral	**Keveyis (dichlorphenamide) may be considered medically necessary when the following criteria are met:** • The individual is aged 18 years or older **AND** • Has a diagnosis of primary hyperkalemic or hypokalemic periodic paralysis **AND** • Documentation of distinct regular episodes of weakness with an average frequency of at least 1 per week **AND** • Normal thyroid-stimulating hormone (TSH) level **AND**

Drug	Medical Necessity
	• Prior therapy with acetazolamide was ineffective, not tolerated, or contraindicated **AND** • Has tried generic dichlorphenamide or Ormalvi (dichlorphenamide) and had an inadequate response or intolerance to dichlorphenamide or Ormalvi (dichlorphenamide) **AND** • The dose is limited to 200 mg daily (4 tablets daily) **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the above conditions are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy as documented by a reduction in number of episodes with weakness per week.
• **Generic dichlorphenamide oral** • **Ormalvi (dichlorphenamide) oral**	**Generic dichlorphenamide and Ormalvi (dichlorphenamide) may be considered medically necessary when the following criteria are met:** • The individual is aged 18 years or older **AND** • Have a diagnosis of primary hyperkalemic or hypokalemic periodic paralysis **AND** • Documentation of distinct regular episodes of weakness with an average frequency of at least 1 per week **AND** • Normal thyroid-stimulating hormone (TSH) level **AND** • Prior therapy with acetazolamide was ineffective, not tolerated, or contraindicated **AND** • The dose is limited to 200 mg daily (4 tablets daily) **Initial therapy may be approved up to 12 months.**

Drug	Medical Necessity
	Re-authorization criteria: • Continued therapy may be approved up to 12 months as long as the above conditions are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy as documented by a reduction in number of episodes with weakness per week.
Sucrase Deficiency	

Sucraid (sacrosidase) oral	**Sucraid (sacrosidase) may be considered medically necessary when the following criteria are met:**
	• The individual has genetically determined sucrase deficiency (which is part of congenital sucrase-isomaltase deficiency)
	AND
	• Diagnosis is confirmed by one of the following:
	  ○ Genetic testing for the sucrase-isomaltase (SI) gene documenting two pathogenic or likely pathogenic variants of the SI gene
	  ○ Disaccharidase assay via small bowel biopsy documenting sucrase activity is below the 10th percentile (less than 25 units)
	AND
	• Receiving a low sucrose, low starch diet
	AND
	• Sucraid (sacrosidase) is prescribed by or in consultation with a gastroenterologist
	AND
	• The dose prescribed is no more than 360 mL every 4 weeks
	
	Initial therapy may be approved up to 12 months.
	
	Re-authorization criteria:
	• Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.

Progeroid Syndromes	

Drug	Medical Necessity

Zokinvy (lonafarnib) oral	**Zokinvy (lonafarnib) may be considered medically necessary when the following criteria are met:**
	• The individual is aged 12 months or older with a body surface area (BSA) of 0.39 m^2 and above*
	AND
	• Diagnosed with 1 of the following:
	  ○ Hutchinson-Gilford progeria syndrome (HGPS)
	  OR
	  ○ Processing-deficient progeroid laminopathies with either:
	  ▪ Heterozygous LMNA mutation with progerin-like protein accumulation
	  OR
	  ▪ Homozygous or compound heterozygous ZMPSTE24 mutations
	AND
	• Dose prescribed is appropriate for individual's BSA
	
	Initial therapy may be approved up to 12 months.
	
	Re-authorization criteria:
	• Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met, chart notes demonstrate that the individual is tolerating therapy, and individual is on appropriate dosage for BSA.
	
	*Zokinvy (lonafarnib) is not indicated in individuals with a BSA less than 0.39 m^2 because the appropriate dosage strength is not available for this population.

Proliferating Infantile Hemangioma	
Hemangeol (propranolol) oral	**Hemangeol (propranolol) may be considered medically necessary for the treatment of proliferating infantile hemangioma when all the following criteria are met:** • The individual has a confirmed diagnosis of proliferating infantile hemangioma that requires systemic therapy **AND** • Dose is limited to 1.7 mg/kg twice daily

Drug	Medical Necessity
	Initial therapy may be approved up to 12 months. **Re-authorization criteria:** • Continued therapy may be approved up to 12 months when the medical necessity criteria are met and chart notes demonstrate that the individual is tolerating and showing a positive clinical response to therapy.
Primary Hyperoxaluria Type 1	

Oxlumo (lumasiran) SC	**Oxlumo (lumasiran) may be considered medically necessary for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary and plasma oxalate levels in pediatric and adult individuals when the following criteria are met:**
	• Diagnosed with PH1 in individuals with 1 of the following:
	  ○ Mutation of the alanine: glyoxylate aminotransferase (AGT or AGXT) gene
	  ○ Liver biopsy demonstrating alanine glycoxylate aminotransferase (AGT) deficiency
	AND
	• Meets 1 of the following:
	  ○ Has a 24-hour urinary oxalate (UOx) excretion of at least 0.7 mmol/24hr/1.73m^2
	  OR
	  ○ If the individual is less than or equal to 5 years of age, an elevated UOx excretion as measured by a spot UOx to creatinine ratio that is above the age-specific upper limit of normal (ULN)
	  OR
	  ○ Has an elevated plasma oxalate (POx) level of at least 20 µmol/L or 1.76 mg/L
	AND
	• The maintenance dose prescribed (begin 1 month after the last loading dose) is limited to:
	  ○ Less than 10 kg: 3 mg/kg once monthly
	  ○ 10 kg to less than 20 kg: 6 mg/kg once every 3 months (quarterly)
	  ○ At least 20 kg: 3 mg/kg every 3 months (quarterly)

Drug	Medical Necessity
	AND • Has not received a liver transplant **AND** • Oxlumo (lumasiran) is prescribed by or in consultation with a nephrologist, urologist, or geneticist **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met, chart notes demonstrate that the individual is tolerating therapy, there is a decrease in urine oxalate or plasma oxalate levels from baseline, and individual is on appropriate dosage for body weight

Rivfloza (nedosiran) SC	**Rivfloza (nedosiran) may be considered medically necessary for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary oxalate levels in pediatric and adult individuals when the following criteria are met:**
	• The individual is aged 2 years or older
	AND
	• Diagnosed with PH1 in individuals with mutation of the alanine: glyoxylate aminotransferase (AGXT) gene
	AND
	• Has an eGFR greater than or equal to 30 mL/min/1.73 m^2
	AND
	• Meets 1 of the following:
	  ○ Has a 24-hour urinary oxalate (UOx) excretion of greater than or equal to 0.7 mmol/24hr/1.73m^2
	  OR
	  ○ Has plasma oxalate (POx) level greater than or equal to 20 µmol/L
	AND
	• The maintenance dose prescribed is limited to:
	  ○ Is aged 12 years and older and greater than or equal to 50 kg: 160 mg once monthly

Drug	Medical Necessity
	○ Is aged 12 years and older and less than 50 kg: 128 mg once monthly ○ Is aged 2 to 11 years and greater than or equal to 50 kg: 160 mg once monthly ○ Is aged 2 to 11 years and 39 kg to less than 50 kg: 128 mg once monthly ○ Is aged 2 to 11 years and less than 39 kg: 3.3 mg/kg once monthly **AND** • Has not received a liver or kidney transplant **AND** • Rivfloza (nedosiran) is prescribed by or in consultation with a nephrologist, urologist, or geneticist **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met, chart notes demonstrate that the individual is tolerating therapy, there is a decrease in urine oxalate or plasma oxalate levels from baseline, and individual is on appropriate dosage for body weight
POMC, PCSK1, or LEPR Deficiency	
Imcivree (setmelanotide) SC	**Imcivree (setmelanotide) may be considered medically necessary to reduce excess body weight in individuals with acquired hypothalamic obesity (HO) when the following criteria are met:** • The individual is aged 4 years or older **AND** • Has documented evidence of acquired HO due to hypothalamic injury or dysfunction (e.g., brain injury, craniopharyngiomas, gliomas) **AND** • Has experienced clinically significant weight gain associated with the hypothalamic injury compared to baseline **AND**

Drug	Medical Necessity

	• Meets 1 of the following:
	  ○ For individuals aged 18 years or older, BMI is at least 30 kg/m^2
	  ○ For individuals aged 4 to 17 years, BMI is at least 95th percentile for age and sex
	AND
	• Imcivree (setmelanotide) is prescribed by or in consultation with an endocrinologist
	AND
	• The dose is limited to 3 mg (0.3 ml) once daily
	AND
	• The quantity is limited to 9 ml per 30 days
	
	Imcivree (setmelanotide) may be considered medically necessary for the treatment of chronic weight management in pediatric and adult individuals with monogenic or syndromic obesity due to POMC, PCSK1, or LEPR deficiency when the following criteria are met:
	• The individual is aged 2 years or older
	AND
	• Obesity is due to variants in 1 of the following genes as confirmed by genetic testing:
	  ○ Proopiomelanocortin (POMC)
	  ○ Proprotein convertase subtilisin/kexin type 1 (PCSK1)
	  ○ Leptin receptor (LEPR)
	AND
	• The genetic test demonstrating variants in POMC, PCSK1, or LEPR genes are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS)*
	AND
	• The baseline weight is:
	  ○ BMI is at least 35 kg/m^2 for adult individuals
	  ○ At least 95th percentile using growth chart assessments for individuals 6 to 17 years of age
	AND

Drug	Medical Necessity

	• Imcivree (setmelanotide) is prescribed by or in consultation with a geneticist or endocrinologist
	AND
	• The dose is limited to 3 mg (0.3 ml) once daily
	AND
	• The quantity is limited to 9 ml per 30 days
	
	Imcivree (setmelanotide) may be considered medically necessary for the treatment of chronic weight management for pediatric and adult individuals with monogenic or syndromic obesity due to Bardet-Biedl syndrome (BBS) when the following criteria are met:
	• The individual is aged 2 years or older
	AND
	• Diagnosed with BBS as confirmed by exhibiting 4 primary symptoms, OR 3 primary symptoms and 2 secondary symptoms:
	  ○ Primary symptoms of BBS: rod-cone dystrophy, polydactyly, obesity, learning disability, hypogonadism in males, renal anomalies
	  ○ Secondary symptoms of BBS: speech disorder/delay, strabismus/cataracts/astigmatism, brachydactyly/syndactyly, developmental delay, polyuria/polydipsia (nephrogenic diabetes insipidus), ataxia/poor coordination/imbalance, mild spasticity (especially lower limbs), diabetes mellitus, dental crowding/hypodontia/small roots/high arched palate, left ventricular hypertrophy/congenital heart disease, hepatic fibrosis
	AND
	• Baseline weight is:
	  ○ BMI at least 35 kg/m^2 for adult individuals
	  ○ At least 97th percentile using growth chart assessments for individuals 6 to 17 years of age
	AND

Drug	Medical Necessity

	• Imcivree (setmelanotide) is prescribed by or in consultation with a geneticist or endocrinologist
	AND
	• The dose is limited to 3 mg (0.3 ml) once daily
	AND
	• The quantity is limited to 9 ml per 30 days
	
	Initial therapy may be approved up to 12 months.
	
	Re-authorization criteria:
	• Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes document:
	  ○ For individuals aged 18 years or older, have lost at least 5% of baseline body weight
	  ○ For individuals aged less than 18 years, the individual shows a positive clinical response to therapy for weight management
	
	Note: Imcivree (setmelanotide) is not indicated in individuals with POMC, PCSK1, or LEPR variants classified as benign or likely benign. Imcivree is not indicated for other types of obesity not related to acquired HO, BBS, or POMC, PCSK1 or LEPR deficiency, including obesity associated with other genetic syndromes and general (polygenic) obesity.

Hemophagocytic Lymphohistiocytosis (HLH)	

Gamifant (emapalumab-lzsg) IV	**Gamifant (emapalumab-lzsg) may be considered medically necessary for the treatment of adult and pediatric individuals when the following criteria are met:**
	• The individual is diagnosed with primary hemophagocytic lymphohistiocytosis (HLH) as confirmed by 1 of the following:
	  ○ Genetic tests for verified HLH-associated mutations (e.g., PRF1, UNC13D, STX11, STXBP2, Rab27A, SH2D1A, BIRC4, LYST, ITK, SLC7A7, XMEN, HPS)
	  ○ Five of the following nine findings:
	  ▪ Fever at least 38.5 degrees Celsius
	  ▪ Splenomegaly

Drug	Medical Necessity
	▪ Peripheral blood cytopenia, with at least 2 of the following: hemoglobin less than 9 g/dL (for infants less than 4 weeks, hemoglobin less than 10 g/dL); platelets less than 100,000/microL; absolute neutrophil count less than 1,000/microL ▪ Hypertriglyceridemia (fasting triglycerides greater than 265 mg/dL) and/or hypofibrinogenemia (fibrinogen less than 150 mg/dL) ▪ Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver ▪ Low or absent NK-cell activity ▪ Ferritin greater than 500 ng/mL ▪ Elevated soluble CD25 ▪ Elevated CXCL9 **AND** • Has tried and failed or was intolerant to conventional therapy (e.g., dexamethasone, hydrocortisone, etoposide, cyclosporine, methotrexate) **AND** • Gamifant (emapalumab-lzsg) is prescribed by or in consultation with a hematologist **Gamifant (emapalumab-lzsg) may be considered medically necessary for the treatment of adult and pediatric individuals when the following criteria are met:** • The individual is diagnosed with hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS) **AND** • Has a confirmed or suspected diagnosis of systemic juvenile idiopathic arthritis (SJIA) or Still's disease **AND** • Has tried and failed or was intolerant to glucocorticoid therapy (e.g., dexamethasone, hydrocortisone) **AND**

Drug	Medical Necessity
	• Gamifant (emapalumab-lzsg) is prescribed by or in consultation with a hematologist **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met, chart notes demonstrate that the individual continues to show a positive clinical response and is tolerating therapy, and a hematopoietic stem cell transplantation (HSCT) has not been performed.
Neuronal Ceroid Lipofuscinoses (NCLs)	

Brineura (cerliponase alfa) intraventricular	**Brineura (cerliponase alfa) may be considered medically necessary to slow the loss of ambulation in pediatric individuals with neuronal ceroid lipofuscinosis type 2 (CLN2) when the following criteria are met:**
	• The individual is aged less than 18 years
	AND
	• Diagnosed with neuronal ceroid lipofuscinosis type 2 (CLN2) (also known as tripeptidyl peptidase 1 [TPP1] deficiency) as confirmed by one of the following:
	  ○ Documented TPP1 enzyme deficiency
	  ○ Genetic testing documenting mutations in the gene encoding TPP1
	AND
	• Brineura (cerliponase alfa) is prescribed by or in consultation with a neurologist or pediatric specialist
	
	Initial therapy may be approved up to 12 months.
	
	Re-authorization criteria:
	• Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.

Castleman's Disease	

Drug	Medical Necessity
Sylvant (siltuximab) IV	**Sylvant (siltuximab) may be considered medically necessary for the treatment of individuals with multicentric Castleman's disease (MCD) when the following criteria are met:** • The individual is aged 18 years or older **AND** • Human immunodeficiency virus (HIV) negative **AND** • Human herpesvirus-8 (HHV-8) negative **AND** • Diagnosed with multicentric Castleman's disease as confirmed by biopsy of lymph node **AND** • Sylvant (siltuximab) is prescribed by or in consultation with a hematologist or oncologist **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response and is tolerating therapy.
Lysosomal Acid Lipase (LAL) Deficiency	

Kanuma (sebelipase alfa) IV	**Kanuma (sebelipase alfa) IV is subject to review for site of service administration.**
	
	Kanuma (sebelipase alfa) may be considered medically necessary for the treatment of lysosomal acid lipase (LAL) deficiency when the following criteria are met:
	• Diagnosed with LAL deficiency as confirmed by 1 of the following:
	  ○ Documented LAL enzyme deficiency
	  ○ Genetic testing documenting mutations in the LIPA gene encoding LAL
	AND
	• Kanuma (sebelipase alfa) is prescribed by or in consultation with an endocrinologist, geneticist, or pediatric specialist

Drug	Medical Necessity
	Initial therapy may be approved up to 12 months. **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes document an improvement from baseline in LDL cholesterol.
Molybdenum Cofactor Deficiency (MoCD) Type A	
Nulibry (fosdenopterin) IV	**Nulibry (fosdenopterin) may be considered medically necessary to reduce risk of mortality in individuals with molybdenum cofactor deficiency (MoCD) Type A when the following criteria are met:** • Diagnosed with MoCD Type A as confirmed by genetic testing documenting mutations in the molybdenum cofactor synthesis 1 gene (MOCS1) **AND** • Nulibry (fosdenopterin) is prescribed by or in consultation with a geneticist, neonatologist, or pediatric specialist **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response and is tolerating therapy.
Paroxysmal Nocturnal Hemoglobinuria	
Voydeya (danicopan) oral	**Voydeya (danicopan) may be considered medically necessary for the treatment of extravascular hemolysis in individuals with paroxysmal nocturnal hemoglobinuria (PNH) when all the following criteria are met:** • The individual is aged 18 years or older **AND** • Diagnosed with PNH confirmed by granulocyte or monocyte clone size of at least 15% **AND**

Drug	Medical Necessity
	• Has completed at least 6 months of therapy with Soliris (eculizumab) or Ultomiris (ravulizumab-cwvz) **AND** • Has experienced residual anemia defined as a hemoglobin less than 10.5 g/dL AND lactic acid dehydrogenase (LDH) level 1.5 times the upper limit of normal while receiving treatment with Soliris (eculizumab) or Ultomiris (ravulizumab-cwvz) **AND** • Voydeya (danicopan) is prescribed in combination with Soliris (eculizumab) or Ultomiris (ravulizumab-cwvz) **AND** • Has received vaccinations against *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* at least 2 weeks prior to initiation of first dose **AND** • Voydeya (danicopan) is prescribed by or in consultation with a hematologist **AND** • The dose is limited to 600 mg daily **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as Voydeya (danicopan) is prescribed by or in consultation with a hematologist and chart notes shows a positive clinical response (e.g., increased or stabilization of hemoglobin levels, reduction in transfusions, improvement in hemolysis, decrease in LDH, or increased reticulocyte count)
Plasminogen Deficiency (PLGD) Type I	
Ryplazim (plasminogen, human-tvmh) IV	**Ryplazim (plasminogen, human-tvmh) may be considered medically necessary for the treatment of individuals with plasminogen deficiency (PLGD) type 1 (hypoplasminogenemia) when the following criteria are met:** • The baseline plasminogen activity level is less than or equal to 45% of normal

Drug	Medical Necessity
	AND • Has documented external lesions and/or internal lesions associated with PLGD prior to Ryplazim treatment **AND** • Ryplazim is prescribed by or in consultation with a hematologist or geneticist **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as Ryplazim is prescribed by or in consultation with a hematologist or geneticist and chart notes shows a positive clinical response as documented by no new or recurrent external lesions and/or internal lesions.
Prader-Willi Syndrome (PWS)	
Vykat XR (diazoxide choline extended-release) oral	**Vykat XR (diazoxide choline extended-release) may be considered medically necessary for the treatment of pediatric and adult individuals with Prader-Willi syndrome when the following criteria are met:** • The individual is aged 4 years or older **AND** • Diagnosis of Prader-Willi syndrome is confirmed by genetic testing **AND** • Dose is limited to 525 mg once daily **AND** • Vykat XR (diazoxide choline extended-release) is prescribed by or in consultation with an endocrinologist **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes document an improvement from baseline in hyperphagia.

Drug	Medical Necessity
Progressive Familial Intrahepatic Cholestasis (PFIC)	

Bylvay (odevixibat) oral	**Bylvay (odevixibat) may be considered medically necessary for the treatment of pruritus in individuals with progressive familial intrahepatic cholestasis (PFIC) when the following criteria are met:**
	• The individual is aged 3 months or older
	AND
	• Has tried ursodiol and 1 of the following for the treatment of pruritus associated with PFIC:
	  ○ Cholestyramine
	  ○ Rifampin
	AND
	• Dose prescribed is limited to 6 mg once daily
	
	Initial therapy may be approved up to 12 months.
	
	Re-authorization criteria:
	• Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes document an improvement from baseline in pruritus.
	
	Note: See the **Alagille syndrome (ALGS) section** for ALGS medical necessity criteria

Alagille Syndrome (ALGS)	

Bylvay (odevixibat) oral	**Bylvay (odevixibat) may be considered medically necessary for the treatment of cholestatic pruritus in individuals with Alagille syndrome (ALGS) when the following criteria are met:**
	• The individual is aged 12 months or older
	AND
	• Has tried ursodiol and 1 of the following for the treatment of pruritus associated with ALGS:
	  ○ Cholestyramine
	  ○ Rifampin
	
	Initial therapy may be approved up to 12 months.

Drug	Medical Necessity
	Re-authorization criteria: • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes document an improvement from baseline in pruritus. **Note:** See the **progressive familial intrahepatic cholestasis (PFIC) section** for the PFIC medical necessity criteria

Livmarli (maralixibat) oral	**Livmarli (maralixibat) may be considered medically necessary for the treatment of pruritus in individuals with Alagille syndrome (ALGS) when the following criteria are met:**
	• The individual is aged 3 months or older
	AND
	• Has tried ursodiol and 1 of the following for the treatment of pruritus associated with ALGS:
	  ○ Cholestyramine
	  ○ Rifampin
	AND
	• Dose prescribed is limited to 28.5 mg once daily
	AND
	• Dose is limited to the following:
	  ○ 9.5 mg/mL oral solution: 90 mL per 30 days
	  ○ 10 mg, 15 mg, 20 mg, and 30 mg tablets: 30 tablets per 30 days
	
	Livmarli (maralixibat) may be considered medically necessary for the treatment of pruritus in individuals with progressive familial intrahepatic cholestasis (PFIC) when the following criteria are met:
	• The individual is aged 12 months or older
	AND
	• Does not have PFIC type 2 with specific ABCB11 variants resulting in nonfunctional or complete absence of bile salt export pump (BSEP) protein
	AND

Drug	Medical Necessity

	• Has tried ursodiol and one of the following for the treatment of pruritus associated with PFIC:
	  ○ Cholestyramine
	  ○ Rifampin
	AND
	• Dose prescribed is limited to 40 mg daily
	AND
	• Dose is limited to the following:
	  ○ 19 mg/mL oral solution: 60 mL per 30 days
	  ○ 10 mg, 15 mg, and 20 mg tablets: 60 tablets per 30 days
	
	Initial therapy may be approved up to 12 months.
	
	Re-authorization criteria:
	• Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes document an improvement from baseline in pruritus.

Polycythemia Vera	

Besremi (ropeginterferon alfa-2b-njft) SC	**Besremi (ropeginterferon alfa-2b-njft) may be considered medically necessary for the treatment of polycythemia vera when the following criteria are met:**
	• The individual is aged 18 years or older
	AND
	• Diagnosis of Polycythemia Vera according to the 2016 WHO criteria as documented by all the following:
	  ○ Hemoglobin greater than 16.5 g/dL(men); Hemoglobin greater than 16.0 g/dL (women) **OR** Hematocrit greater than 49% (men); Hematocrit greater than 48% (women) **OR** increased red cell mass (RCM) more than 25% above mean normal predicted value
	  AND
	  ○ BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
	  AND

Drug	Medical Necessity
	○ Presence of JAK2 or JAK2 exon 12 mutation OR subnormal serum erythropoietin level **AND** • The dose is limited to 500 mcg every 2 weeks **AND** • The quantity is limited to 2 pens or syringes every 28 days **Initial therapy may be approved up to 24 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months if blood work documents all the following: ○ Hematocrit less than 45% ○ Platelets less than or equal to 400 x 10^9/L ○ Leukocytes less than or equal to 10 x 10^9/L
Achondroplasia (ACH)	
Voxzogo (vosoritide) SC	**Voxzogo (vosoritide) may be considered medically necessary for the treatment of achondroplasia when the following criteria are met:** • The individual has been diagnosed with achondroplasia confirmed by genetic testing (FGFR3 gene mutation) **AND** • Has evidence of open epiphyses OR a Tanner Stage less than 4 **AND** • Has evidence of growth velocity of at least 1.5 centimeters in the last 12 months **AND** • Does not have planned or expected limb-lengthening surgery **AND** • Voxzogo (vosoritide) is not used concurrently with Yuviwel (navepegritide) **AND** • The dose prescribed is appropriate based on the individual's actual body weight ○ 10-11 kg = 0.24 mg once daily ○ 12-16 kg = 0.28 mg once daily ○ 17-21 kg = 0.32 mg once daily

Drug	Medical Necessity
	○ 22-32 kg = 0.4 mg once daily ○ 33-43 kg = 0.5 mg once daily ○ 44-59 kg = 0.6 mg once daily ○ 60-89 kg = 0.7 mg once daily ○ At least 90 kg = 0.8 mg once daily **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy will be approved if the individual's growth plates are still open and individual has grown at least 1.5 cm in the past year
Yuviwel (navepegritide) SC	**Yuviwel (navepegritide) may be considered medically necessary to increase linear growth in individuals with achondroplasia when all of the following criteria are met:** • The individual is aged 2 years or older **AND** • Has been diagnosed with achondroplasia confirmed by genetic testing (FGFR3 gene mutation) **AND** • Has evidence of open epiphyses OR a Tanner Stage less than 4 **AND** • Does not have planned or expected limb-lengthening surgery **AND** • Yuviwel (navepegritide) is not used concurrently with Voxzogo (vosoritide) **AND** • The dose prescribed is appropriate based on the individual's actual body weight: ○ 8-9.9 kg = 0.88 mg weekly ○ 10-13.4 kg = 1.2 mg weekly ○ 13.5-17.5 kg = 1.6 mg weekly ○ 17.6-23 kg = 2.1 mg weekly ○ 23.1-30.5 kg = 2.8 mg weekly ○ 30.6-41.2 kg = 3.6 mg weekly ○ 41.3-55.9 kg = 5 mg weekly ○ 56-73.5 kg = 6.6 mg weekly

Drug	Medical Necessity
	○ 73.6-90 kg = 8.8 mg weekly **AND** • The quantity is limited to: ○ 1.3 mg and 2.8 mg vials = 4 vials per 28 days ○ 5 mg vials = 8 vials per 28 days **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy will be approved if the individual's growth plates are still open and individual has grown at least 1.5 cm in the past year
Cold Agglutinin Disease (CAD)	
Enjaymo (sutimlimab-jome) IV	**Enjaymo (sutimlimab-jome) may be considered medically necessary to decrease the need for red blood cell (RBC) transfusion due to hemolysis in adults with cold agglutinin disease (CAD) when the following criteria are met:** • The individual is aged 18 years or older **AND** • Has a confirmed diagnosis of CAD **AND** • Does NOT have cold agglutinin syndrome (e.g., secondary to infection, rheumatologic disease, active hematologic malignancy) **AND** • Hemoglobin level is less than or equal to 10.0 g/dL **AND** • Bilirubin level above normal reference range, including individuals with Gilbert's syndrome **AND** • Tried and failed rituximab (either as monotherapy or as combination therapy) unless contraindicated **AND** • Enjaymo is not used in combination with rituximab **AND**

Drug	Medical Necessity
	• Received vaccinations against Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenzae at least 2 weeks prior to initiation of first dose **AND** • Enjaymo is prescribed by or in consultation with a hematologist **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met, chart notes demonstrate that the individual is tolerating therapy and there is an increase from baseline in Hgb level.
Pyruvate Kinase (PK) Deficiency	

Pyrukynd (mitapivat) oral	**Pyrukynd (mitapivat) may be considered medically necessary for the treatment of hemolytic anemia in adults with pyruvate kinase deficiency (PKD) when the following criteria are met:**
	• The individual is aged 18 years or older
	AND
	• Has a diagnosis of PKD with at least two mutant alleles in the PKLR (pyruvate kinase liver and red blood cell) gene, of which at least one is a missense mutation
	AND
	• One documented red blood cell (RBC) transfusion within the past 12 months
	AND
	• Hemoglobin level is less than or equal to 10.0 g/dL
	AND
	• Does NOT have any of the following:
	  ○ Homozygous for the R479H mutation
	  ○ Double non-missense mutations
	  ○ Recent history (12 months or less) of splenectomy
	  ○ Known history of bone marrow/stem cell transplantation
	AND
	• Dose prescribed is limited to 100 mg daily (taken as 50 mg twice daily)

Drug	Medical Necessity
	AND • Pyrukynd is prescribed by or in consultation with a hematologist **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met, chart notes demonstrate that the individual is tolerating therapy, and documentation of: ○ An increase in hemoglobin level from baseline **AND/OR** ○ Reduction in RBC transfusions from baseline
Acid Sphingomyelinase Deficiency (ASMD)	
Xenpozyme (olipudase alfa-rpcp) IV	**Xenpozyme (olipudase alfa-rpcp) may be considered medically necessary for treatment of non–central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) in adult and pediatric individuals when the following criteria are met:** • Confirmation of chronic neurovisceral ASMD (Niemann-Pick disease [NPD] A/B or NPD B variant, or NPD B) or chronic visceral ASMD (NPD B) via ASMD biochemical enzyme assay **AND** • Gene sequencing documenting a genetic abnormality in SMPD1 **AND** • For individuals aged 18 years and older, the diffusing capacity for carbon monoxide (DLCO) is less than or equal to 70% than the predicted normal value **AND** • The dose prescribed is limited to 3 mg/kg* (recommended maintenance dose) administered every 2 weeks **Initial therapy may be approved up to 12 months.**

Drug	Medical Necessity
	Re-authorization criteria: • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy. **Note:** *The recommended maintenance dose is based on body weight as follows for individuals with a body mass index (BMI): (1) Less than or equal to 30, the dosage is based on actual body weight (kg); (2) Greater than 30, the dosage is based on adjusted body weight (kg). The calculated adjusted body weight (kg) = (actual height in m)^2 x 30.
Friedreich's Ataxia	
Skyclarys (omaveloxolone) oral	**Skyclarys (omaveloxolone) may be considered medically necessary for the treatment of Friedreich's ataxia when the following criteria are met:** • The individual is aged 16 years or older **AND** • Diagnosed with Friedreich's ataxia as confirmed by genetic testing that documents a mutation in the frataxin (FXN) gene **AND** • Is ambulatory without assistance **AND** • The dose prescribed is no more than 150 mg once daily **AND** • Skyclarys (omaveloxolone) is prescribed by or in consultation with a neurologist **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.
Alpha-Mannosidosis	

Drug	Medical Necessity
Lamzede (velmanase alfa-tycv) IV	**Lamzede (velmanase alfa-tycv) may be considered medically necessary for treatment of non-central nervous system manifestations of alpha-mannosidosis when ALL the following are met:** • The individual has a diagnosis of alpha mannosidosis confirmed by bi-allelic pathogenic variants in the *MAN2B1* gene **AND** • Has a documentation of less than 10% of normal alpha-mannosidase activity in blood leukocytes **AND** • Does not have neurological symptoms (e.g., cognitive impairment or impaired speech) **AND** • Is able to ambulate without support **AND** • Has not received a hematopoietic stem cell transplant or bone marrow transplant **AND** • The dose is limited to 1 mg/kg weekly **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.
Cerebrotendinous Xanthomatosis (CTX)	
Ctexli (chenodiol) oral	**Ctexli (chenodiol) may be considered medically necessary for the treatment of cerebrotendinous xanthomatosis (CTX) when ALL the following are met:** • The individual is aged 18 years or older **AND** • Has a diagnosis of CTX confirmed by genetic testing that detected disease-causing variants in the CYP27A1 gene

Drug	Medical Necessity
	AND • Biochemical testing indicates a high plasma cholestanol concentration (5 to 10 times normal levels) with a normal to low plasma cholesterol concentration **AND** • Will not be used concomitantly with Cholbam (cholic acid) **AND** • Dose is limited to 750 mg daily **AND** • Prescribed by, or in consultation with, a neurologist, endocrinologist, or other metabolic specialists **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy defined as a reduction in the individual's plasma cholestanol or urine 23S-pentol levels compared to baseline.
Congenital Adrenal Hyperplasia	
Crenessity (crinecerfont) oral	**Crenessity (crinecerfont) may be considered medically necessary for treatment of classic congenital adrenal hyperplasia (CAH) when ALL the following are met:** • The individual is aged 4 years or older **AND** • Has a diagnosis of classic CAH due to 21-hydroxylase deficiency **AND** • Has a mean 17-hydroxyprogesterone (17-OHP) level greater than 8,000 ng/dL **AND** • Weighs at least 10 kg **AND**

Drug	Medical Necessity
	• Requires a total glucocorticoid dose greater than 12 mg/m^2/day in hydrocortisone dose equivalents if aged less than 18 years OR greater than 13 mg/m^2/day in hydrocortisone dose equivalents if aged 18 years or older **AND** • There is documentation of a medical need to decrease the individual's daily glucocorticoid dose **AND** • If aged less than 18 years, the androstenedione (A4) level prior to the morning glucocorticoid dose is greater than the midpoint of the **reference range** according to the individual's gender assigned at birth and either their age if the individual is Tanner stage 1 or pubertal age if the individual is Tanner stage 2 to 5 **AND** • Will use the capsule formulation OR there is documentation that the oral solution is medically necessary (e.g., trouble swallowing) **AND** • Dose is limited to 200 mg daily **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy defined as a reduction in the individual's daily glucocorticoid dose compared to baseline.
Rett Syndrome	
• **Daybue (trofinetide) oral solution** • **Daybue Stix (trofinetide) oral solution powder**	**Daybue (trofinetide) and Daybue Stix (trofinetide) may be considered medically necessary for the treatment of Rett syndrome when the following criteria are met:** • The individual is aged 2 years or older **AND**

Drug	Medical Necessity

	• Diagnosed with Rett Syndrome as confirmed by genetic testing that documents a mutation in MECP2 gene
	AND
	• The dose prescribed is appropriate based on the individual's weight:
	  ○ 9 kg – less than 12 kg = 5,000 mg twice daily
	  ○ 12 kg – less than 20 kg = 6,000 mg twice daily
	  ○ 20 kg – less than 35 kg = 8,000 mg twice daily
	  ○ 35 kg – less than 50 kg = 10,000 mg twice daily
	  ○ More than 50 kg = 12,000 mg twice daily
	AND
	• The quantity is limited to:
	  ○ Daybue solution = 3600 ml per 30 days
	  ○ Daybue Stix 5,000 mg and 6,000 mg = 120 packets per 30 days
	  ○ Daybue Stix 8,000 mg = 60 packets per 30 days
	
	Initial therapy may be approved up to 12 months.
	
	Re-authorization criteria:
	Continued therapy may be approved for up to 12 months, as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy, and documentation of:
	• Improvement on the Rett Syndrome Behavior Questionnaire (RSBQ) score from baseline
	OR
	• Improvement on the Clinical Global Impression-Improvement (CGI-I) score from baseline

Bile Acid Synthesis Disorders	
Cholbam (cholic acid) capsule	**Cholbam (cholic acid) may be considered medically necessary for the treatment of bile acid synthesis disorders due to single enzyme defects (SED) when the following criteria are met:** • The individual has a confirmed diagnosis of SED **AND** • Will not be used concomitantly with Ctexli (chenodiol)

Drug	Medical Necessity
	AND • Cholbam is prescribed by or in consultation with a hepatologist, metabolic specialist, or a gastroenterologist **Cholbam (cholic acid) may be considered medically necessary for the adjunctive treatment of peroxisomal disorders (PDs) including Zellweger spectrum disorders when the following criteria are met:** • The individual has a diagnosis of peroxisomal disorders including Zellweger spectrum disorder **AND** • Has liver disease, steatorrhea, or complications from decreased fat-soluble vitamin absorption **AND** • Will not be used concomitantly with Ctexli (chenodiol) **AND** • Cholbam is prescribed by or in consultation with a hepatologist, metabolic specialist, or a gastroenterologist **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.
Fibrodysplasia Ossificans Progressiva	
Sohonos (palovarotene) capsule	**Sohonos (palovarotene) may be considered medically necessary for reduction in the volume of new heterotopic ossification in adults and children with fibrodysplasia ossificans progressiva (FOP) when the following criteria are met:** • The individual is a female aged 8 years or older or male aged 10 years or older **AND**

Drug	Medical Necessity
	• Has a documented activin A receptor type 1 (ACVR1) R206H mutation confirmed by genetic testing **AND** • For individuals of reproductive potential, attestation that the individual is NOT pregnant and has been informed that appropriate forms of contraception should be implemented 1 month prior to initiation, during treatment, and for 1 month following the last dose of Sohonos **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.
WHIM Syndrome	
Xolremdi (mavorixafor) oral	**Xolremdi (mavorixafor) may be considered medically necessary to increase the number of circulating mature neutrophils and lymphocytes in individuals with warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome when all the following criteria are met:** • The individual is aged 12 years or older **AND** • Diagnosed with WHIM syndrome as confirmed by pathogenic or likely pathogenic variants in the *CXCR4* gene **AND** • Has an absolute neutrophil count (ANC) is less than or equal to 400 cells/µL **AND** • Has experienced symptoms associated with WHIM syndrome **AND** • The dose is limited to 400 mg daily **AND** • Xolremdi (mavorixafor) is prescribed by or in consultation with an immunologist or hematologist

Drug	Medical Necessity
	Initial therapy may be approved up to 12 months. **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy including sustained improvement in ANC and absolute lymphocyte count (ALC)
Niemann-Pick Disease Type C (NPC)	

Aqneursa (levacetylleucine) oral	**Aqneursa (levacetylleucine) may be considered medically necessary for the treatment of neurological manifestations of Niemann-Pick disease type C (NPC) in adult and pediatric individuals when all the following criteria are met:**
	• The individual is aged 4 years or older and weighs at least 15 kg
	AND
	• Diagnosis of NPC1 or NPC2 is confirmed by genetic testing documenting one of the following:
	  ○ Mutations in both alleles of NPC1 or NPC2
	  ○ Mutation in one allele AND either a positive filipin-staining or cholestane-triol level (more than 2× ULN)
	AND
	• One or more neurological signs of NPC disease (e.g., poor swallowing, speech deficit)
	AND
	• Able to ambulate independently or assisted
	AND
	• Aqneursa (levacetylleucine) is not used in combination with Miplyffa (arimoclomol)
	AND
	• Aqneursa (levacetylleucine) is prescribed by or in consultation with a specialist in pediatric neurology, a movement disorder specialist, or clinical geneticist specializing in NPC management
	AND

Drug	Medical Necessity

	• The dose prescribed is appropriate based on the individual's weight:
	  ○ At least 15 kg – less than 25 kg = 1 gram twice daily
	  ○ At least 25 kg – less than 35 kg = 1 gram three times a day
	  ○ At least 35 kg = 4 grams a day taken as 2 grams in the morning, 1 gram in the afternoon, and 1 gram in the evening
	
	Initial therapy may be approved up to 12 months.
	
	Re-authorization criteria:
	• Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy as documented by an improvement or stabilization from baseline in ambulation, fine motor skills, swallowing, or speech.

Miplyffa (arimoclomol) oral	**Miplyffa (arimoclomol) may be considered medically necessary for the treatment of neurological manifestations of Niemann-Pick disease type C (NPC) in adult and pediatric individuals when all the following criteria are met:**
	• The individual is aged 2 years or older
	AND
	• Diagnosis of NPC1 or NPC2 is confirmed by genetic testing documenting one of the following:
	  ○ Mutations in both alleles of NPC1 or NPC2
	  ○ Mutation in one allele AND either a positive filipin-staining or cholestane-triol level (greater than 2× ULN)
	AND
	• One or more neurological signs of NPC disease (e.g., poor swallowing, speech deficit)
	AND
	• Able to ambulate independently or assisted
	AND
	• Miplyffa (arimoclomol) is used in combination with miglustat
	AND

Drug	Medical Necessity
	• Miplyffa (arimoclomol) is not used in combination with Aqneursa (levacetylleucine) **AND** • Miplyffa (arimoclomol) is prescribed by or in consultation with a specialist in pediatric neurology, a movement disorder specialist, or clinical geneticist specializing in NPC management **AND** • The dose prescribed is appropriate based on the individual's weight: o At least 8 kg - 15 kg = 47 mg three times a day o More than 15 kg - 30 kg = 62 mg three times a day o More than 30 kg - 55 kg = 93 mg three times a day o More than 55 kg = 124 mg three times a day **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy as documented by an improvement or stabilization from baseline in ambulation, fine motor skills, swallowing, or speech.
Generic miglustat, Yargesa (generic miglustat) oral	**Generic miglustat and Yargesa (generic miglustat) may be considered medically necessary when used in combination with Miplyffa (arimoclomol) for the treatment of neurological manifestations of Niemann-Pick disease type C (NPC) in adult and pediatric individuals when all the following criteria are met:** • The individual is aged 2 years or older **AND** • Diagnosis of NPC1 or NPC2 is confirmed by genetic testing documenting one of the following: o Mutations in both alleles of NPC1 or NPC2 o Mutation in one allele AND either a positive filipin-staining or cholestane-triol level (more than 2× ULN) **AND**

Drug	Medical Necessity
	• One or more neurological signs of NPC disease (e.g., poor swallowing, speech deficit) **AND** • Able to ambulate independently or assisted **AND** • Generic miglustat or Yargesa (generic miglustat) is used in combination with Miplyffa (arimoclomol) **AND** • Generic miglustat or Yargesa (generic miglustat) is prescribed by or in consultation with a specialist in pediatric neurology, a movement disorder specialist, or clinical geneticist specializing in NPC management **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy as documented by an improvement or stabilization from baseline in ambulation, fine motor skills, swallowing, or speech. **Note:** See the **Gaucher disease section** for the Gaucher disease medical necessity criteria
Opfolda (miglustat) oral	**Opfolda (miglustat) may be considered medically necessary when used in combination with Miplyffa (arimoclomol) for the treatment of neurological manifestations of Niemann-Pick disease type C (NPC) in adult and pediatric individuals when all the following criteria are met:** • The individual is aged 2 years or older **AND** • Diagnosis of NPC1 or NPC2 is confirmed by genetic testing documenting one of the following: ○ Mutations in both alleles of NPC1 or NPC2

Drug	Medical Necessity
	○ Mutation in one allele AND either a positive filipin-staining or cholestane-triol level (more than 2× ULN) **AND** • One or more neurological signs of NPC disease (e.g., poor swallowing, speech deficit) **AND** • Able to ambulate independently or assisted **AND** • Opfolda (miglustat) is used in combination with Miplyffa (arimoclomol) **AND** • Opfolda (miglustat) is prescribed by or in consultation with a specialist in pediatric neurology, a movement disorder specialist, or clinical geneticist specializing in NPC management **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy as documented by an improvement or stabilization from baseline in ambulation, fine motor skills, swallowing, or speech. **Note:** See the **Gaucher disease section** for the Gaucher disease medical necessity criteria
Zavesca (miglustat) oral	**Zavesca (miglustat) may be considered medically necessary when used in combination with Miplyffa (arimoclomol) for the treatment of neurological manifestations of Niemann-Pick disease type C (NPC) in adult and pediatric individuals when all the following criteria are met:** • The individual is aged 2 years or older **AND** • Diagnosis of NPC1 or NPC2 is confirmed by genetic testing documenting one of the following:

Drug	Medical Necessity
	○ Mutations in both alleles of NPC1 or NPC2 ○ Mutation in one allele AND either a positive filipin-staining or cholestane-triol level (more than 2× ULN) **AND** • One or more neurological signs of NPC disease (e.g., poor swallowing, speech deficit) **AND** • Able to ambulate independently or assisted **AND** • Zavesca (miglustat) is used in combination with Miplyffa (arimoclomol) **AND** • Medical records indicate that the individual has tried and failed generic miglustat **AND** • Brand Zavesca is being requested due to a formulation difference in the inactive ingredient(s) [e.g., preservatives] between the brand and the bioequivalent generic product, which, per the prescribing physician has or would result in a significant allergy or serious adverse reaction. **AND** • Zavesca (miglustat) is prescribed by or in consultation with a specialist in pediatric neurology, a movement disorder specialist, or clinical geneticist specializing in NPC management **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy as documented by an improvement or stabilization from baseline in ambulation, fine motor skills, swallowing, or speech.

Drug	Medical Necessity
	Note: See the **Gaucher disease section** for the Gaucher disease medical necessity criteria
Menkes Disease	

Zycubo (copper histidinate) SC	**Zycubo (copper histidinate) may be considered medically necessary when used for the treatment of Menkes disease in pediatric individuals when all the following criteria are met:**
	• The individual is less than 17 years of age
	AND
	• Diagnosis of Menkes disease is confirmed by documenting 1 of the following:
	  ○ Genetic testing showing presence of ATP7A variants in the mother and/or child
	  ○ Plasma catecholamine analysis consistent with diagnosis:
	  ▪ Dopamine/norepinephrine ratio greater than 0.2
	  ▪ Dihydroxyphenylacetic acid/dihydroxyphenylglycol ratio greater than 5.0
	AND
	• Presence of neurological symptoms and clinical findings suggestive of Menkes disease (e.g., loss of early developmental milestones, hypotonia, seizures, failure to thrive occur, unusual hair [short, sparse, coarse, twisted, lightly pigmented], jowly appearance of the face, transient hypoglycemia, prolonged physiologic jaundice, persistent temperature instability)
	AND
	• The individual does not have Occipital Horn Syndrome
	AND
	• Zycubo (copper histidinate) is initiated by 6 weeks of age, corrected for prematurity or gestational age
	AND
	• Zycubo (copper histidinate) is prescribed by or in consultation with a geneticist or neurologist
	AND
	• The dose prescribed is appropriate based on the individual's age:
	  ○ Younger than 1 year of age: 1.45 mg twice daily

Drug	Medical Necessity
	○ 1 year of age to less than 17 years of age: 1.45 mg once daily **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.
Barth Syndrome	
Forzinity (elamipretide) SC	**Forzinity (elampretide) may be considered medically necessary when used to improve muscle strength in adult and pediatric individuals with Barth syndrome when all the following criteria are met:** • The individual is aged 12 years or older **AND** • The individual weighs at least 30 kg **AND** • Diagnosis of Barth syndrome is confirmed by genetic testing documenting a pathogenetic variant in the *TAZ* gene **AND** • Forzinity (elamipretide) is prescribed by or in consultation with a pediatric cardiologist or hematologist **AND** • The dose is limited to 40 mg daily **Initial therapy may be approved up to 12 months.** **Re-authorization criteria:** • Continued therapy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy as documented by improvement in baseline muscle strength.

Drug	Investigational
As listed	**The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**All drugs listed in the policy, unless noted otherwise for specific drugs under the medical necessity criteria, may be approved up to 12 months.**
Re-authorization criteria	**All drugs listed in the policy may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.**

Coding

Code	Description
HCPCS	
G0138	Intravenous infusion of cipaglucosidase alfa-atga, including provider/supplier acquisition and clinical supervision of oral administration of miglustat in preparation of receipt of cipaglucosidase alfa-atga (Opfolda with Pombiliti)
J0180	Injection, agalsidase beta (Fabrazyme), 1 mg
J0217	Injection, velmanase alfa-tycv (Lamzede), 1 mg
J0218	Injection, olipudase alfa-rpcp (Xenpozyme), 1 mg
J0219	Injection, avalglucosidase alfa-ngpt (Nexviazyme), 4 mg
J0221	Injection, alglucosidase alfa (Lumizyme), 10 mg
J0223	Injection, givosiran (Givlaari), 0.5 mg
J0224	Injection, lumasiran (Oxlumo), 0.5 mg
J0567	Injection, cerliponase alfa (Brineura), 1 mg
J0584	Injection, burosumab-twza (Crysvita), 1 mg

Code	Description
J1202	Miglustat (Opfolda), oral, 65 mg
J1203	Injection, cipaglucosidase alfa-atga (Pombiliti), 5 mg
J1302	Injection, sutimlimab-jome (Enjaymo), 10 mg
J1322	Injection, elosulfase alfa (Vimizim), 1 mg
J1458	Injection, galsulfase (Naglazyme) 1 mg
J1743	Injection, idursulfase (Elaprase), 1 mg
J1786	Injection, imiglucerase (Cerezyme), 10 units
J1809	Injection, fosdenopterin (Nulibry), 0.1 mg
J1931	Injection, laronidase (Aldurazyme), 0.1 mg
J2508	Injection, pegunigalsidase alfa-iwxj (Elfabrio), 1 mg
J2840	Injection, sebelipase alfa (Kanuma), 1 mg
J2860	Injection, siltuximab (Sylvant), 10 mg
J2998	Injection, plasminogen, human-tvmh (Ryplazim), 1 mg
J3060	Injection, taliglucerase alfa (Elelyso), 10 units
J3241	Injection, teprotumumab-trbw (Tepezza), 10 mg
J3385	Injection, velaglucerase alfa (Vpriv), 100 units
J3397	Injection, vestronidase alfa-vjbk (Mepsevii), 1 mg
J3490	Unclassified drugs (use to report: Rivfloza)
J3590	Unclassified biologics (Use to report: Cablivi, Besremi, Imcivree, Revcovi, and Voxzogo)
J9210	Injection, emapalumab-lzsg (Gamifant), 1 mg

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Definition of Terms

3-minute stair climb test: Measures total time to ascend and descend steps in a period of 3 minutes. It evaluates functional strength, balance, and agility. It is also a preoperative tool to identify individuals at increased risk for lung resection.

6-minute walk distance test (6MWD): The test measures the distance that an individual can quickly walk on flat, hard surface in a period of 6 minutes. It evaluates global and integrated responses of all the systems involved during exercise, including cardiovascular, pulmonary, peripheral circulation, neuromuscular units, and muscle metabolism.

12-minute walk distance (12MWD): Like the 6-minute walk test, this tool measures the distance an individual can quickly walk in a period of 12 minutes.

Antigenic levels of α1-PI: The maintenance of blood serum levels of α1-PI above 11 μM that is thought to provide therapeutically relevant antineutrophil elastase protection

Forced vital capacity (FVC): The total volume exhaled during pulmonary function test

Functional levels of α1-PI: Level of α1-PI to neutralize porcine pancreatic elastase

GL-3 Inclusion Score: Measure of globotriaosylceramide (GL3) in renal interstitial capillary endothelial cells assessed by light microscopy. Inclusion severity score ranges from 0 (normal) to 3 (severe inclusions).

Consideration of Age

Age limits specified in this policy are determined according to the US Food and Drug Administration (FDA)-approved indications, where applicable.

For site of service for medical necessity the age described in this policy is 13 years of age or older. Site of service is defined as the location where the drug is administered, such as a hospital-based outpatient setting, an infusion center, a physician's office, or at home. The age criterion for site of service for medical necessity is based on the following: Pediatric individuals are not small adults. Pediatric individuals differ physiologically, developmentally, cognitively, and emotionally from adult individuals, and vary by age groups from infancy to teen. Children often require smaller doses than adults, lower infusion rates, appropriately sized equipment, the right venipuncture site determined by therapy and age, and behavioral management during administration of care. Specialty infusion training is therefore necessary for pediatric IV

insertions and therapy. Due to pediatrics unique physiology and psychology, site of service review is limited to individuals above the age of 13.

The ages listed in the policy statements are based on FDA labeling for each drug:

- Crenessity: The safety of Crenessity in individuals younger than 4 years of age has not been evaluated.
- Fabrazyme: The safety of Fabrazyme in individuals younger than 2 years of age has not been evaluated.
- Elfabrio: The safety of Elfabrio has not been established in individuals younger than 18 years of age.
- Lumizyme: The safety and effectiveness of alglucosidase alpha has been established in pediatric individuals. Clinical trials for infantile-onset Pompe disease included individuals 0.2 months old to 3.5 years old.
- Vpriv: The safety of Vpriv has not been established in pediatric individuals younger than 4 years of age.
- Elaprase: Elaprase has been shown to improve walking capacity in individuals 5 years and older.
- Crysvita: Crysvita is indicated for the treatment of X-liked hypophosphatemia (XLH) in adult and pediatric individuals 6 months of age and older and FGF23-related hypophosphatemia in tumor induced osteomalacia (TIO) for pediatric individuals 2 years of age and older.
- Vimizim: The safety and effectiveness of Vimizim have not been established in pediatric individuals less than 5 years of age.
- Imcivree: The safety and effectiveness of Imcivree have not been established in pediatric individuals less than 2 years of age.
- Skyclarys: The safety and effectiveness of Skyclarys have not been established in individuals younger than 16 years of age.
- Daybue: The safety and effectiveness of Daybue have not been established in individuals younger than 2 years of age.
- Rivfloza: The safety and effectiveness of Rivfloza has not been established in individuals younger than 2 years of age.

- Pombiliti and Opfolda: The safety and effectiveness of Pombiliti and Opfolda has not been established in individuals younger than 18 years of age.
- Voydeya: The safety and effectiveness of Voydeya has not been established in individuals younger than 18 years of age.
- Xolremdi: The safety and effectiveness of Xolremdi has not been established in individuals younger than 12 years of age.

Benefit Application

Pharmacy Benefit

Aqneursa (levacetylleucine), Aqvesme (mitapivat), betaine anhydrous, Bylvay (odevixibat), Cerdelga (eliglustat), Cholbam (cholic acid), Crenessity (crinecerfont), Ctexli (chenodiol), Cystadane (betaine anhydrous), dichlorphenamide, Daybue (trofinetide), Daybue Stix (trofinetide), Dojolvi (triheptanoin), Firdapse (amifampridine), Forzinity (elamipretide), Galafold (migalastat), Gattex (teduglutide), Hemangeol (propranolol), Keveyis (dichlorphenamide), Kygevvi (doxecitine and doxribtimine), Livmarli (maralixibat), miglustat, Miplyffa (arimoclomol), Opfolda (miglustat), Ormalvi (dichlorphenamide), Pyrukynd (mitapivat), Skyclarys (omaveloxolone), Sohonos (palovarotene), Sucraid (sacrosidase), Voydeya (danicopan), Vykat XR (diazoxide choline extended-release), Xolremdi (mavorixafor), Xuriden (uridine triacetate), Yargesa (generic miglustat), Yorvipath (palopegteriparatide), Yuviwel (navepegritide), Zavesca (miglustat), Zokinvy (lonafarnib), and Zycubo (copper histidine) are managed through the pharmacy benefit.

Medical Benefit

Aldurazyme (laronidase), Brineura (cerliponase alfa), Cerezyme (imiglucerase), Crysvita (burosumab), Elaprase (idursulfase), Elelyso (taliglucerase alfa), Enjaymo (sutimlimab), Elfabrio (pegunigalsidase alfa-iwxj), Fabrazyme (agalsidase beta), Gamifant (emapalumab-lzsg), Kanuma (sebelipase alfa), Lamzede (velmanase alfa-tycv), Lumizyme (alglucosidase alfa), Mepsevii (vestronidase alfa), Naglazyme (galsulfase), Nexviazyme (avalglucosidase alfa-ngpt), Nulibry (fosdenopterin), Pombiliti (cipaglucosidase alfa-atga), Revcovi (elapegademase-lvlr), Rivfloza (nedosiran), Ryplazim (plasminogen, human-tvmh), Sylvant (siltuximab), Tepezza (teprotumumab-trbw), Vimizim (elosulfase alfa), Vpriv (velaglucerase alfa), and Xenpozyme (olipudase alfa-rpcp) are managed through the medical benefit.

Medical / Pharmacy Benefit

Besremi (ropeginterferon alfa-2b-njft), Cablivi (caplacizumab-yhdp), Givlaari (givosiran), Imcivree (setmelanotide), Oxlumo (lumasiran), and Voxzogo (vosoritide) are managed through both the pharmacy and medical benefit.

Serum Androstenedione (A4) Reference Range

Gender Assigned at Birth	Serum Androstenedione (A4) Reference Range
Female	• 1-11 months: ≤ 41 ng/dL; ≤ 1.4309 nmol/L • 1 year: ≤ 35 ng/dL; ≤ 1.2215 nmol/L • 2 years: ≤ 34 ng/dL; ≤ 1.1866 nmol/L • 3 years: ≤ 38 ng/dL; ≤ 1.3262 nmol/L • 4 years: ≤ 42 ng/dL; ≤ 1.4658 nmol/L • 5 years: ≤ 45 ng/dL; ≤ 1.5705 nmol/L • 6 years: ≤ 45 ng/dL; ≤ 1.5705 nmol/L • 7 years: ≤ 48 ng/dL; ≤ 1.6752 nmol/L • 8 years: ≤ 57 ng/dL; ≤ 1.9893 nmol/L • 9 years: ≤ 77 ng/dL; ≤ 2.6873 nmol/L • 10 years: 15-111 ng/dL; 0.5235-3.8739 nmol/L • 11 years: 24-149 ng/dL; 0.8376-5.2001 nmol/L • 12 years: 32-182 ng/dL; 1.1168-6.3518 nmol/L • 13 years: 37-205 ng/dL; 1.2913-7.1545 nmol/L • 14 years: 42-221 ng/dL; 1.4658-7.7129 nmol/L • 15 years: 46-238 ng/dL; 1.605-8.3062 nmol/L • 16 years: 50-252 ng/dL; 1.745-8.7948 nmol/L • 17 years: 53-265 ng/dL; 1.8497-9.2485 nmol/L • Tanner Stages II-III: 43-180 ng/dL; 1.5007-6.282 nmol/L • Tanner Stages IV-V: 73-220 ng/dL; 2.5477-7.6678 nmol/L
Male	• 1-11 months: ≤ 41 ng/dL; ≤ 1.4309 nmol/L • 1 year: ≤ 31 ng/dL; ≤ 1.0819 nmol/L • 2 years: ≤ 27 ng/dL; ≤ 0.9423 nmol/L • 3 years: ≤ 27 ng/dL; ≤ 0.9423 nmol/L • 4 years: ≤ 29 ng/dL; ≤ 1.0121 nmol/L • 5 years: ≤ 31 ng/dL; ≤ 1.0819 nmol/L • 6 years: ≤ 36 ng/dL; ≤ 1.2564 nmol/L • 7 years: ≤ 43 ng/dL; ≤ 1.5007 nmol/L • 8 years: ≤ 54 ng/dL; ≤ 1.8846 nmol/L • 9 years: ≤ 65 ng/dL; ≤ 2.2685 nmol/L • 10 years: 10-77 ng/dL; 0.349-2.6873 nmol/L

Gender Assigned at Birth	Serum Androstenedione (A4) Reference Range
	• 11 years: 12-90 ng/dL; 0.4188-3.141 nmol/L • 12 years: 14-106 ng/dL; 0.4886-3.6994 nmol/L • 13 years: 17-124 ng/dL; 0.5933-4.3276 nmol/L • 14 years: 19-139 ng/dL; 0.6631-4.8511 nmol/L • 15 years: 21-154 ng/dL; 0.7329-5.3746 nmol/L • 16 years: 24-172 ng/dL; 0.8376-6.0028 nmol/L • 17 years: 27-192 ng/dL; 0.9423-6.7008 nmol/L • Tanner Stages II-III: 17-82 ng/dL; 0.5933-2.8618 nmol/L • Tanner Stages IV-V: 57-150 ng/dL; 1.9893-5.235 nmol/L

Conversion Factor from ng/dL to nmol/L: x 0.0349

Evidence Review

Fabrazyme (agalsidase beta)

Background on Fabry Disease

Fabry disease results from abnormal deposits of a particular fatty substance (called globotriaosylceramide) in blood vessel walls throughout the body. The primary defect which allows this to occur is the inherited deficiency of the enzymes, alpha galactosidase A, which is normally responsible for the breakdown of globotriaosylceramide. As the abnormal storage of this fatty compound increases with time, the channels of these vessels become narrowed, leading to decreased blood flow and decreased nourishment of the tissues normally supplied by these vessels. This abnormal process occurs in blood vessels through the body, particularly affecting vessels in the skin, kidneys, heart, brain, and nervous system. Common features of Fabry disease include episodes of pain, angiokeratomas, hypohidrosis, corneal opacity, hearing loss. Life-threatening symptoms include progressive kidney damage, heart attack, and stroke.

Fabry disease is diagnosed by a low measurement of leukocyte alpha-Gal A activity in classically affected males. In females or males with atypical presentations, genetic testing is recommended in males or females with marginal levels of alpha-Gal A activity. If no other means of diagnosis are available, biopsy of skin or culture of skin fibroblast may be helpful in establishing diagnosis.

Primary treatment is enzyme replacement therapy with Fabrazyme (agalsidase beta).

Summary of Evidence for Fabrazyme (agalsidase beta)

The safety and efficacy of Fabrazyme (agalsidase beta) were assessed in 4 clinical studies in individuals with Fabry disease. Fabrazyme is indicated for use in individuals with Fabry disease.

Study 1 was a randomized, double-blind, placebo-controlled, multi-national, multi-center study consisting of 58 individuals who are enzyme treatment-naïve.[1] Individuals were randomized to receive either 1 mg/kg of Fabrazyme or placebo every other week for five months. The primary efficacy endpoint of GL-3 inclusions in renal interstitial capillary endothelial cells was assessed by light microscopy and was graded on an inclusion severity score ranging from 0 (normal or near normal) to 3 (severe inclusions). In the Fabrazyme group, 69% of subjects achieved GL-3 inclusion score of 0 compared to 0% in the placebo group ($p<0.001$)

Study 2 was a randomized-controlled, double-blind, placebo-controlled, multi-national, multi-center study of 82 subjects.[2] Individuals were randomized 2:1 to receive 1 mg/ kg Fabrazyme or placebo every two weeks for up to 35 months, respectively. The primary endpoint was the time to first clinical event (renal, cardiac, cerebrovascular event, or death). The study showed 42% of placebo group and 27% of Fabrazyme group experienced a clinical event. The primary intent-to-treat analysis showed that the hazard ratio of Fabrazyme compared to placebo adjusted for imbalance in baseline proteinuria was 0.47 (95% CI: 0.21 to 1.03; $p=0.06$). The most treatment-related adverse reactions were rigors (35%), fever (27%), and hypertension (14%). Only 3 deaths occurred in the study. There was a significant decrease in post-baseline plasma GL-3 levels in the Fabrazyme-treated individuals compared to placebo. The reduction was significant at one year ($p<0.0001$) and two years ($p=0.0019$). There was also statistically significant reduction in mean plasma GL-3 levels from baseline in the additional 18 months of treatment in the extension study.

Study 3 was an open-label, multi-national, multi-center pediatric study to evaluate the safety and tolerability in 16 pediatric individuals with Fabry disease.[3] No primary endpoints were specified. All 16 individuals achieved normal plasma GL-3 levels at week 48. Overall safety and efficacy profile of Fabrazyme treatment in pediatric individuals was found to be consistent with that seen in adults. No new safety concerns were identified in the pediatric study. More than 90% of adverse events were mild or moderate in severity. The most frequently reported infusion reactions were rigors (14%), fever (9%), and rhinitis (8%) in individuals receiving Fabrazyme.

Study 4 was an open-label, re-challenge study to evaluate the safety of Fabrazyme treatment in individuals who had a positive skin test to Fabrazyme or who had tested positive for Fabrazyme-specific IgE antibodies.[4] Six individuals were evaluated for up to 52 weeks. Four of the six individuals received at least 26 weeks of Fabrazyme and two individuals discontinued prematurely due to recurrent infusion reactions.

Regulatory Status of Fabrazyme (agalsidase beta)

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

Fabry disease is an X-linked genetic disorder. However, some heterozygous women will develop signs and symptoms of Fabry disease due to the variability of the X-chromosome inactivation within cells. A total of 12 adult female individuals with Fabry disease were enrolled in two separate randomized, double-blind, placebo-controlled clinical studies with Fabrazyme, and two female pediatric individuals with Fabry disease, ages 11 years, were evaluated in an open-label, uncontrolled pediatric study. Although the safety and efficacy data available in female individuals in these clinical studies are limited, there is no indication that female individuals respond differently to Fabrazyme compared to males.

Elfabrio (pegunigalsidase alfa-iwxj)

Summary of Evidence for Elfabrio (pegunigalsidase alfa-iwxj)

The safety and efficacy of Elfabrio (pegunigalsidase alfa-iwxj) was investigated through four clinical trials involving individuals diagnosed with Fabry disease. Elfabrio is indicated for the treatment of adults with confirmed Fabry disease.

Study 1 was a phase 1/2, open-label, parallel assignment, and dose-ranging trial was conducted to evaluate the safety, tolerability, pharmacokinetics, and exploratory efficacy parameters of Elfabrio in eighteen adult individuals diagnosed with Fabry disease. During this trial, participants received either a 0.2mg/kg intravenous (IV) infusion of Elfabrio every 2 weeks or Elfabrio 1 mg/kg IV infusion every 2 weeks or 2 mg/kg IV infusion every 2 weeks for total of 12 weeks. It is important to note that dosages of 0.2 mg/kg and 2 mg/kg are not approved and not recommended. Participants who completed this study were then enrolled in an extension study that continued for an additional 38 weeks. The inclusion criteria for this trial included individuals who were naïve to enzyme replacement therapy (ERT) or had not received ERT for more than 26 weeks, with negative test for anti-pegunigalsidase alfa-iwxj IgG antibodies prior to enrollment. Out of participants in the 1 mg/kg group, two individuals discontinued the study, with one of them experiencing severe hypersensitivity reaction. The primary outcome of the study focused on assessing the number of adverse events considered possibly, probably, or definitely related to the treatment. Additionally, other outcomes measured included the concentration of plasma

glabotriaosylceramide (Gb3) concentrations at baseline and every 3 months up to 12 months. The average number of Gb3 inclusions per renal peritubular capillary (PTC) in renal biopsy specimens of individuals was assessed by light microscopy using the quantitative Barisoni Lipid Inclusion Scoring System (BLISS). At week 26, the mean change in Renal biopsy BLISS score was recorded as -3.1.

Study 2 was a randomized, double-blind, and active-controlled trial designed to compare the safety and efficacy of Elfabrio with agalsidase beta on the renal function in individuals with Fabry disease who had previously received treatment with agalsidase beta for at least one year. A total of 77 individuals were randomized 2:1 to receive Elfabrio 1mg/kg IV infusion or agalsidase beta 1mg/kg IV infusion every two weeks for 104 weeks. The inclusion criteria of the study mandated that participants be between 18 and 60 years old and display characteristic features of Fabry disease. The primary efficacy endpoint of the trial focused on assessing the annualized rate of change in estimated GFR (eGFR slope) over the course of 104 weeks. The estimated mean eGFR slope was -2.4 ml/min/1.73m^2/year in the Elfabrio arm and -2.3 ml/min/1.73m^2/year in the agalsidase beta arm. The estimated treatment difference between two groups was -0.1 ml/min/1.73m^2/year (95% CI: -2.3,2.1).

Study 3 was a phase 3, open-label, switch-over study conducted to evaluate the safety, efficacy, and pharmacokinetics of Elfabrio 2mg/kg administered every 4 weeks for 52 weeks in Fabry disease individuals who were currently undergoing treatment with other enzyme replacement therapies (ERT), such as Fabrazyme or Replagal. The study included 30 individuals ranging in age from 18 to 60 years, all of whom exhibited characteristic features of Fabry disease. Male individuals were required to have plasma and/or leucocyte alpha galactosidase activity below the lower limit of normal, while female individuals needed to have a historical test consistent with the Fabry mutation. The most common Fabry disease symptoms at baseline included acroparesthesia, heat intolerance, angiokeratomas and hyperhidrosis. Out of the 30 participants, 29 individuals completed the study, with 28 individuals receiving a dose of 2 mg/kg of Elfabrio and one individual receiving 1 mg/kg of Elfabrio per protocol. At the end of week 52, the plasma lyso-Gb3 concentrations remained stable, showing a mean change of 3.01 nM from baseline. Similarly, the absolute eGFR values stayed stable, showing a mean change of -1.27 ml/min/1.73m^2. The mean eGFR slope for overall population at the end of the study was -2.92 ml/min/1.73m^2/year. Throughout the study, there were no severe or serious treatment-emergent adverse events (TEAEs), and none of the treatment-emergent adverse events led to death or study withdrawal. The majority of TEAEs were related to infusion-related reactions (IRRs).

Study 4 was an open-label study conducted to evaluate the safety and efficacy of Elfabrio in individuals diagnosed with Fabry disease who had been receiving treatment with Replagal for at least 2 years. The inclusion criteria specified an age range of 18 to 60 years with a documented

diagnosis of Fabry disease. The primary efficacy endpoint of the study focused on the presence of treatment-emergent anti-PRX-102 antibodies at month 12. All participants received Elfabrio1 mg/kg every 2 weeks. Out of the 20 individuals who completed the study, seven individuals tested positive for IgG anti-penguingalsidase alfa anti-drug antibodies at least at one time point. Additional efficacy endpoints assessed changes in the plasma Lyso-Gb3 and the mean annualized eGFR slope. At month12, the mean concentration of plasma lyso-Gb3 decreased from baseline by 31.5% compared to baseline, and the mean annualized eGFR slope improved from -5.90 ml/min/1.73m^2 for agalsidase alfa to -1.19 ml/min/1.73m^2 for Elfabrio.

Regulatory Status of Elfabrio (pegunigalsidase alfa-iwxj)

Elfabrio (pegunigalsidase alfa-iwxj) is indicated for the treatment of adults with confirmed diagnosis of Fabry disease. Elfabrio functions as an exogenous source of enzyme alpha-galactosidase A. Elfabrio is designed to be transported into the lysosome, where it is believed to exert enzymatic activity and reduce the accumulation of Gb3.

In the clinical trials, the most observed adverse effects were infusion-associated reactions, followed by nasopharyngitis, headache, diarrhea, fatigue, and nausea. Notably, there were clinically significant adverse reactions such as hypersensitivity reactions including anaphylaxis, infusion-associated reactions and membranoproliferative Glomerulonephritis.

Lumizyme (alglucosidase alfa)

Background on Pompe Disease

Pompe disease is an autosomal recessive metabolic disorder that damages muscle and nerve cells through the body. The etiology is the accumulation of glycogen in lysosome due to deficiency of lysosomal acid α-glucosidase (GAA) enzyme. Clinical presentation can vary from asymptomatic to severe, progressive myopathy. Juvenile and adult form of Pompe disease presents with primarily skeletal myopathy with more protracted course leading to respiratory failure. Survival is highly dependent on the onset of disease. Untreated pediatric individuals with infantile form of Pompe disease live up to 8.7 months due to cardiorespiratory failure. Adult form of the disease have better prognosis. Individuals who are cross-reactive immunologic material (CRIM)-negative are associated with increased risk of death or invasive ventilation after 52 weeks of therapy.

Gene sequencing with findings of two pathogenic mutations in trans in the GAA gene confirms the diagnosis of Pompe disease. Measurement of GAA activity in muscle obtained by biopsy or measurement of GAA enzyme activity in white blood cells or dried blood spots are an alternative diagnostic tool but is not preferred. Prenatal diagnosis can be measured by cultured amniocytes or chorionic villus samples.

The primary treatment for Pompe disease is enzyme replacement therapy with Lumizyme (alglucosidase alfa).

Summary of Evidence for Lumizyme (alglucosidase alfa)

The safety and efficacy of Lumizyme (alglucosidase alfa) was assessed in three separate clinical trials. Lumizyme is a hydrolytic lysosomal glycogen-specific enzyme indicated for individuals with Pompe disease (GAA deficiency).

Study 1 was an international, multi-center, open-label clinical study. Infant subjects (N=61) who were 7 months of age or younger with clinical signs of Pompe disease and cardiac hypertrophy and did not require ventilator support were randomized 1:1 in receive either 20 mg/kg or 40 mg/kg Lumizyme every other week for 52 to 106 weeks.[5] Fourteen of individuals were CRIM-positive and 4 individuals were CRIM-negative. The primary efficacy outcome was proportion of Lumizyme-treated individuals who died or needed ventilator support at 18 months of age. About 83% of Lumizyme-treated individuals were alive without ventilator support and 17% required invasive ventilator support whereas 2% of the historical control was alive. There were no differences in outcome observed between the two doses of Lumizyme.

Study 2 was an international, multicenter, non-randomized, open-label clinical trial that enrolled 21 infantile-onset individuals aged 3 months to 3.5 years at first infusion.[5] All individuals received 20 mg/kg Lumizyme for up to 104 weeks. Eighteen individuals were CRIM-positive and 3 individuals were CRIM-negative. The primary outcome was the proportion of individuals alive at the end of treatment. Seventy-six percent of the individuals were alive at week 52 and 24% were receiving ventilator support.

Study 3 was an open-label, single-center trial in 18 infantile-onset individuals with Pompe disease identified through a newborn screening program. Individuals were treated prior to 6 months of age. All the individuals were CRIM-positive. At the primary analysis, 89% of individuals reached 18 months of age and all individuals were alive without invasive ventilator support.

Two multicenter, open-label trials were conducted in 39 infantile-onset Pompe disease individuals who received Lumizyme. The most common adverse reactions in 51% of individuals were hypersensitivity reaction, which included rash, pyrexia, urticaria, flushing, and hypertension.

Pombiliti (cipaglucosidase alfa-atga) and Opfolda (miglustat)

Pombiliti (cipaglucosidase alfa-atga) and Opfolda (miglustat) is a two-part therapy consisting of Pombiliti, an intravenous (IV) enzyme replacement therapy, and Opfolda, an oral enzyme stabilizer. The safety and efficacy of Pombiliti and Opfolda were evaluated in the Phase 3 randomized, double-blind, activecontrolled PROPEL trial (NCT03729362). In the trial, both enzyme replacement therapy-experienced and -naïve adult individuals with late-onset Pompe disease were randomized to receive Pombiliti and Opfolda or alglucosidase alfa. Individuals treated with Pombiliti and Opfolda in the overall population walked on average 21 meters farther from baseline as compared to those treated with alglucosidase alfa product and placebo, who walked 8 meters farther from baseline; the estimated treatment difference of 14 meters was not statistically significant (95% CI: −1, 28). Individuals treated with Pombiliti and Opfolda in the overall population showed a mean change in sitting forced vital capacity (FVC) from baseline at Week 52 of −1.1% as compared with individuals treated with alglucosidase alfa and placebo of −3.3%; the estimated treatment difference of 2.3% was statistically significant (95% CI: 0.02, 4.62). The most frequently reported treatment-emergent adverse events (TEAEs) were fall (29% of individuals in the Pombiliti and Opfolda group versus 39% in the alglucosidase alfa and placebo group), headache (24% versus 24%), nasopharyngitis (22% versus 8%), myalgia (16% versus 13%), and arthralgia (15% versus 13%). Twelve serious adverse events (SAEs) occurred in eight individuals in the Pombiliti and Opfolda group.

Background on Gaucher's Type I Disease

Gaucher's Type I disease is an autosomal recessive disorder of glucocerebrosidase enzyme deficiency which leads to lipid accumulation in bones and organs. Presentation is variable. Some individuals present before 24 months of age, whereas others have no symptoms until adulthood with liver and spleen enlargement, anemia, fatigue, reduced platelets, bone pain. The prevalence is estimated to be 1 in 50,000 to 100,000 people. The life expectancy is approximately 68 years.

Diagnosis of Gaucher's disease is confirmed by finding reduced glucocerebrosidase activity, usually in peripheral leukocytes, in individuals with clinical features consistent of Gaucher's disease. Mutation analysis provides additional confirmation of diagnosis. The presence of

Gaucher's cells in bone marrow in individuals who are evaluated for splenomegaly, anemia, or thrombocytopenia can often diagnose disease, but not necessary. Prenatal diagnosis is performed by enzyme analysis of fetal cells obtained by chorionic villus sampling or amniocentesis.

Primary treatment options are enzyme replacement therapy, Cerezyme (imiglucerase), Vpriv (velaglucerase alfa), Elelyso (taliglucerase alfa), or Cerdelga (eliglustat).

Cerezyme (imiglucerase)

Summary of Evidence for Cerezyme (imiglucerase)

Clinical evidence of Cerezyme (imiglucerase) is based on a clinical trial. Cerezyme is indicated for long-term enzyme replacement therapy for pediatric and adult individuals with a confirmed diagnosis of Type 1 Gaucher's disease that results in one or more of the following conditions: anemia, thrombocytopenia, bone disease, or hepatomegaly or splenomegaly.

In the clinical trial, RC 91-0110, is a double-blind, randomized, parallel group study which evaluated 30 subjects naïve to enzyme replacement therapy.[6] Thirty subjects were randomized to receive 60 U/kg Cerezyme or Ceredase (alglucerase injection) intravenously once every two weeks for six months. Primary efficacy outcomes evaluated at baseline increase in hemoglobin concentration, increase in platelet counts, and decrease in liver volume. The study showed statistical increase in hemoglobin and platelet and decrease in liver volume in both treatment groups. There was no significant difference between individuals who received Cerezyme and Ceredase. The most commonly reported treatment-related adverse reactions were fever, dizziness, pruritus, and headache. Most adverse reactions were mild in intensity.

Regulatory Status of Cerezyme (imiglucerase)

Cerezyme (imiglucerase) is indicated for long-term enzyme replacement therapy for pediatric and adult individuals with a confirmed diagnosis of Type 1 Gaucher's disease that results in one or more of the following conditions: anemia, thrombocytopenia, bone disease, hepatomegaly, or splenomegaly.

It is also not known whether Cerezyme can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity.

The safety and effectiveness of Cerezyme (imiglucerase for injection) have been established in individuals between 2 and 16 years of age. Use of Cerezyme in this age group is supported by evidence from adequate and well-controlled studies of Cerezyme and Ceredase (alglucerase injection) in adults and pediatric individuals, with additional data obtained from the medical literature and from long-term post-marketing experience.

Vpriv (velaglucerase alfa)

Summary of Evidence for Vpriv (velaglucerase alfa)

Clinical evidence of Vpriv (velaglucerase alfa) was assessed in three clinical studies. Vpriv is indicated for long-term enzyme replacement therapy (ERT) for pediatric and adult individuals with type 1 Gaucher's disease.

Study 1 was a randomized, double-blind, parallel-dose, multi-national study in 25 treatment-naïve subjects aged 4 and older with Gaucher's disease-related anemia and either thrombocytopenia or organomegaly. Individuals were randomized in either 45 U/kg or 60 U/kg Vpriv every other week for 12 months. The study evaluated change in hemoglobin at 12 months from baseline as the primary endpoint. The study demonstrated statistically significant ($p<0.001$) increase in hemoglobin in the 60 U/kg (increase in 2.4 g/dL from baseline). In other endpoints, the study also demonstrated statistically significant increase in platelets and decrease in liver volume and spleen volume in both treatment arms. Rate of adverse reactions were similar across both treatment arms. Serious adverse events include grand mal convulsion, which only manifested in subjects receiving 60 U/kg Vpriv.

Study 2 was a randomized, double-blind, active-controlled, parallel-group, multinational study in 34 individuals aged 3 or older with Gaucher's disease-related anemia or either thrombocytopenia or organomegaly. Individuals who received disease-specific therapy for at least the previous 12 months were excluded. Subjects were randomized into either 60 U/kg Vpriv or 60 U/k g Cerezyme every other week. The primary endpoint was mean change in hemoglobin at 9 months from baseline. The study showed a mean absolute increase of 1.6 g/dL and 1.4 g/dl from baseline in the respective Vpriv and Cerezyme group. Serious adverse reactions included thrombocytopenia, convulsions, and dermatitis. The study showed serious adverse reactions in the Vpriv group. The most commonly report adverse reactions in ≥10% of individuals in the Vpriv group were pyrexia, arthralgia, headache, paresthesia, cough, urticaria, pruritus, peripheral edema, diarrhea, cystitis, influenza, rhinitis, tinea versicolor, urinary tract infection, hypersensitivity.

Study 3 was an open-label, single-arm, multi-national study in 40 subjects aged 9 or older who are treatment-experienced with Cerezyme for a minimum of 30 consecutive months. Subjects were switched over to Vpriv once every other week after minimum of 6 months therapy with Cerezyme. The primary endpoint evaluated was individuals who experienced at least one adverse reaction. The study showed that 85% of individuals had one or more adverse reactions while on treatment. The most common adverse reactions reported were headache (30%), nasopharyngitis (20%), arthralgia (20%), and back pain 18%). After 12 months of treatment with Vpriv the median hemoglobin concentration was 13.5 g/dL (compared to 13.8 g/dL at baseline) and the median platelet count was 174 x 10^9/L (compared to 162 x 10^9/L.

The evidence of safety was based on five clinical studies in 54 treatment-naïve individuals and 40 Cerezyme-experienced individuals. The most commonly adverse reactions reported in more than 10 percent of individuals that were considered related to Vpriv were infusion-related reactions (51.9%), headache (35.2%), dizziness (22.2%), and abdominal pain (18.5%). The most commonly reported serious reactions were hypersensitivity reactions. All adult adverse reactions were considered relevant to pediatric individuals. Adverse reactions more commonly seen in pediatric individuals compared to adult individuals (≥10% of individuals) were upper respiratory tract infection, rash, prolonged aPTT, and pyrexia.

Regulatory Status of Vpriv (velaglucerase alfa)

Vpriv (velaglucerase alfa) is a hydrolytic lysosomal glucocerebroside-specific enzyme indicated for long-term enzyme replacement therapy (ERT) for pediatric and adult individuals with type 1 Gaucher's disease. Individuals currently being treated with imiglucerase for type 1 Gaucher's disease may be switched to Vpriv.

The safety and effectiveness of Vpriv have been established in individuals between 4 and 17 years of age. Use of Vpriv in this age group is supported by evidence from adequate and well controlled studies of Vpriv in adults and pediatric [20 of 94 (21%)] individuals. The safety and efficacy profiles were similar between pediatric and adult individuals. The safety of Vpriv has not been established in pediatric individuals 6 years younger than 4 years of age.

Background on Mucopolysaccharidosis Type II

MPS type II (MPS II) is an X-linked disorder caused by a mutation in the iduronate 2-sulfate (IDS) gene located on chromosome Xq28. Deficiency of IDS results in accumulation of heparin and dermatan sulfate. Clinical presentation of severe disease can include abnormal facial

appearance, enlarged spleen, cardiac abnormalities, neurocognitive decline, and deafness. The onset of clinical presentations is at 1 or 2 years. The prevalence of MPS II is 0.29 out of 100,000 newborns. The prognosis of the attenuated form of the disease has a slower clinical course with normal intelligence and survival up to 60-70 years.

Primary treatment is enzyme replacement therapy (ERT) with Elaprase (idursulfase). Although somatic improvements have occurred in severe individuals, cognitive benefits have not been shown due to ERT not crossing the blood brain barrier.

Elaprase (idursulfase)

Summary of Evidence for Elaprase (idursulfase)

Evidence of Elaprase (idursulfase) is based on two clinical studies. Elaprase (idursulfase) is indicated for individuals with Hunter syndrome (Mucopolysaccharidosis II, MPS II).

Study 1 was a randomized, double-blinded, placebo-controlled clinical trial of 96 individuals with MPS II age 5 and older. Individuals were randomized into Elaprase 0.5 mg/kg once weekly, Elaprase 0.5 mg/kg once every other week or placebo. The primary efficacy endpoint evaluated was a composite score based on sums of the change from baseline to week 53 in 6-minute walk test and change in percent predicted FVC. At primary analysis, Elaprase weekly increased 44.3 meters (p=0.01), Elaprase every other week increased by 30.3 meters (p=0.07), and placebo increased by 7.3 meters. For percent predicted FVC, 3.45%, 0.004% and 0.75% increase was shown in individuals receiving Elaprase weekly, Elaprase every other week, and placebo group, respectively. The most frequently reported adverse events included fever, headache, cough, pharyngitis, upper respiratory tract infection, nasal congestion, nausea, vomiting, abdominal pain, and diarrhea. Most adverse reactions were mild to moderate in intensity. Two deaths occurred during the study. Forty-six percent of individuals developed IgG anti-idursulfase antibodies.

Study 2 was an open-label, multi-center, single-arm trial in male individuals aged 7 and younger to receive Elaprase 0.5 mg/kg once weekly.[12] This study evaluated safety and tolerability of Elaprase 0.5 mg/kg once weekly for 53 weeks. Individuals experienced similar adverse reactions as those observed in clinical trials in individuals 5 years and older, with the most common adverse reactions being hypersensitivity reactions. The most common serious adverse reactions occurring in at least 10% of individuals included pneumonia (18%), ear infection (11%), and pyrexia (11%). Safety results demonstrate that individuals with complete gene deletion or large gene rearrangement mutations are more likely to develop antibodies, including neutralizing

antibodies. Of the 15 individuals, 100% of individuals developed anti-idursulfase antibodies and 87% developed anti-idursulfase neutralizing antibodies.

Regulatory Status of Elaprase (idursulfase)

Elaprase (idursulfase) is a hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme indicated for individuals with Hunter syndrome (Mucopolysaccharidosis II, MPS II). Elaprase has been shown to improve walking capacity in individuals 5 years and older. In individuals 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 individuals, less than 16 months of age.

Elaprase includes a boxed warning for life-threatening anaphylactic reactions, presenting as respiratory distress, hypoxia, hypotension, urticaria, and/or angioedema of throat or tongue.

Background on X-Linked Hypophosphatemia (XLH)

XLH is the most common cause of heritable rickets. The incidence of XLH is 3.9-5 births per 100,000 live births. The diagnosis of XLH is most commonly made around ages 1-2 as lower extremity bowing occurs due to weight bearing and walking. However, milder cases may not be diagnosed until adulthood. The most common presentation of XLH is bowing deformities of the legs in childhood as well as antero-medial rotational torsion of the tibiae and short stature. Joint pain and impaired mobility are common in adults due to enthesopathy or calcification of the tendons, ligaments, and joint capsules. Severe osteomalacia, arthritis, stress fractures, and pseudofractures also occur. Other reported symptoms include cranial abnormalities (frontal bossing, craniosynostosis, and Chiari malformations), spontaneous dental abscesses due to defective mineralization, and hearing loss due to osteosclerosis of the petris bone. Common complications of XLH included dental disease (63%), nephrocalcinosis (42%), and hearing impairment (14%). Overall, 42% of individuals reported ≥1 osteotomy, 20% noted osteoarthritis of the hip, and 12% osteoarthritis of the knee.

Common laboratory abnormalities seen with XLH include low serum phosphate concentration and reduced tubular resorption of phosphate corrected for glomerular filtration rate. Alkaline phosphatase is elevated in children and typically returns to normal in adults. Elevated 1,25 (OH)2 vitamin D, the normal response to hypophosphatemia, is absent and serum calcium and 25-hydroxy vitamin D are normal. The principal abnormality of XLH is renal phosphate wasting,

leading to decreased mineralization of the long bones and teeth. Impaired proximal renal tubular reabsorption of phosphate occurs due to reduced ex-pression of sodium-phosphate cotransporters NaPi-IIA and NapI-IIc (type II sodium-phosphate symporters) in proximal renal tubule. Elevated levels of the hormone FGF23 which suppresses transcription of the genes encoding the sodium-phosphate cotransports found in individuals with XLH.[10] FGF23 binds to renal tubular cells; however, it is not known how this results in reduced expression of sodium-phosphate cotransporters. FDF23 also down regulates CYP271B and upregulates CYP24A1, resulting in low to normal levels of 1,25 (OH)2D.

XLH results from mutations in the PHEX gene (Phosphate regulating gene with Homology to Endopeptidases located on the X chromosome). PHEX codes an endopeptidase which activates or degrades peptides and is involved in bone and dentin mineralization. PHEX leads to reduced expression of FGF23 although the mechanism is not known. Therefore, PHEX mutations result in increased FGF23.

The goal of therapy is to improve pain and correct bone deformation. Treatment in children includes oral phosphate therapy and high-dose calcitriol, typically until growth is complete. Titration of phosphate is required to minimize abdominal pain and diarrhea. Normalization of serum phosphate is not a goal as this is associated with overtreatment complications. Overall, treatment may partially correct leg deformities, decrease surgeries, and improve adult height, although early initiation is key, and height may not correct. Adverse events seen with treatment include the risk of nephrocalcinosis, hypercalciuria, and hyperparathyroidism. Growth hormones have also been used to stimulate phosphate reabsorption; however, long-term results are variable. Treatment of XLH in adults is reserved for those with skeletal pain, upcoming orthopedic surgery, osteomalacia, and recurrent pseudofractures or stress fractures. There is no evidence that oral phosphate and calcitriol alter long-term complications of XLH in adults.

Summary of Evidence for Crysvita (burosemab)

Crysvita (burosemab) was studied in 2 pediatric open-label, 64-week Phase 2 trials. The pediatric trials were designed to assess changes in severity of rickets. Overall, 13 individuals aged 1-4 years and 52 individuals aged 5-12 years were included for a total of 65 children. No adolescents were included. The primary outcomes were the Thacher rickets severity score (RSS), a 10-point scale assessing severity of rickets via radiographic evidence at a single time point, and the radiographic global impression of change (RGI-C), a radiographic evaluation of rickets severity over time with higher scores indicating improved healing. Both trials found significant improvements in RSS and RGI-C with burosumab compared to baseline (RSS decreased 58%-59%, $p<0.0001$for both comparisons. In the second study, growth velocity increased 0.56

cm/year (p=0.0376) and standing height Z score improved 0.19 (p<0.0001). Measures of functionality showed significant improvement with burosumab compared to baseline including a 4.5% improvement in walking distance (p<0.0001).

Burosumab was assessed in a randomized, double-blind, placebo-controlled, 24-week, Phase 3 trial in 134 adults with XLH and skeletal pain. Individuals were randomized to burosumab 1 mg/kg Q4W or placebo. The primary outcome measure was the proportion of individuals with mean serum phosphorous levels greater than the lower limit of normal (2.5 mg/dL) at the midpoint of the dosing interval. Significantly more burosumab than placebo individuals met the primary endpoint at 24 weeks (94.1% vs 7.6%, p<0.0001). Of 156 active or pseudofractures identified at baseline, 50% of active fractures and 41% of pseudofractures were healed at 24 weeks in the burosumab group compared to 0% and 9% with placebo. The rate of new fractures was not assessed. Significant improvements were also noted with burosumab compared to placebo at 24 weeks for mean stiffness and physical function (p=0.01 and 0.0478, respectively); however, pain did not differ significantly between groups (p=0.09). An on-going trial extension of the Phase 3 trial with results to 48 weeks found significant improvements in physical function and fracture healing continued with burosumab. Opioid use decreased from 25% to 6% and nonsteroidal anti-inflammatory drug (NSAID) use decreased from 69% to 19% at week 48. Lastly, a small, open-label, single-arm trial in adults with XLH found burosumab improved markers of osteomalacia at 48 weeks compared to baseline.

Overall burosumab was well tolerated. Injection site reactions occurred commonly (12% of adults and 59% of children) but were considered mild. Other common AEs included back pain, headache, tooth infection, and restless leg syndrome (RLS) in adults, and headache, vomiting, and pyrexia in children. No individuals discontinued any of the trials due to AEs. Serious AEs possibly related to treatment included a dental abscess, angioedema with concomitant lisinopril, and a hospitalization due to muscle pain/fever.

Background on Mucopolysaccharidosis Type IVA

MPS Type IVA (MPS IVA) results from mutations in gene encoding galactosamine-6-sulfatase (GALNS), located at 16q24.[3] Deficiency of GALNS leads to accumulations of GAGs, keratin sulfate and chondroitin-6-sulfate, and results in cell and organ damage. The prevalence of MPS IVA I is estimated to be 0.22 per 100,000 births. The disorder is characterized by skeletal involvement, most notably short stature, spinal cord complications, and respiratory problems. Vision problems, enlarged spleen, and valvular heart disease may occur. Survivability of individuals is an average of 20 to 30 years without treatment and can live up to 70 years. Shortened lifespan is due to respiratory obstruction, cervical spinal cord complication, or heart valve diseases.

Vimizim (elosulfase alfa)

Summary of Evidence for Vimizim (elosulfase alfa)

Evidence of Vimizim (elosulfase alfa) is based on a clinical trial. Vimizim is indicated for individuals with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome).

In a randomized, double-blinded, placebo-controlled clinical trial, 176 individuals with MPS IVA age 5 and older were randomized into either Vimizim 2 mg/kg once weekly group, Vimizim 2 mg/kg once every other week, or placebo group.[13] The primary efficacy endpoint was change from baseline in the 6-minute walk test at week 24. Compared to placebo (9.9 m), Vimizim once weekly regimen had a 20-meter increase from baseline at week 24 in the 6-minute walking test (p=0.02). The most commonly reported adverse reactions in at least 10% of individuals in the individuals receiving Vimizim were pyrexia (33%), vomiting (31%), headache (26%), nausea (24%), and abdominal pain (21%).

Regulatory Status of Vimizim (elosulfase alfa)

Vimizim (elosulfase alfa) is indicated for individuals with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome). Vimizim includes a boxed warning for life-threatening anaphylactic reactions. There are no adequate and well-controlled studies in pregnant women.

Background on Primary Periodic Paralysis (PP)

The primary periodic paralysis (PP) are rare autosomal-dominant disorders associated with skeletal muscle sodium, potassium, and calcium channel gene mutations. Characteristic symptoms include episodes of muscle weakness associated with variations in serum potassium levels. The primary PP are classified as hyperkalemic PP (hyperPP), hypokalemic PP (hypoPP), and Andersen's syndrome (AS; Platt and Griggs, 2009).

HyperPP is characterized by attacks of flaccid limb paralysis with weakness associated with abnormally elevated serum potassium levels up to 6 mEq/L. Triggers for these attacks are ingestion of potassium-rich food, rest after strenuous exercise, and cold exposure. Episodes of weakness may last for up to an hour and disappear as the blood potassium concentration decreases. Attacks typically begin in the first decade of life, increase in frequency and severity

during puberty, and then decrease in frequency after 40 years of age. Myotonia of the extremities supports the diagnosis of hyperPP.

Hypokalemic PP is generally characterized by reversible attacks of muscle weakness associated with decreased blood potassium concentrations below 3.2 mEq/L. In the most severe cases the blood potassium concentration decrease below 1 mEq/L during the attacks. The attacks are triggered by rest after strenuous exercise, by a meal rich in carbohydrates, or by exposure to cold. The glucose-dependent insulin release from pancreatic beta cells or insulin injection is one of the most effective provocative factors in the human disease. Individuals typically wake up paralyzed, and attacks usually last several hours to days in the severe cases. In the elderly, the individuals develop progressive, persistent weakness that takes the form of a proximal myopathy.

Andersen's syndrome is characterized by a unique phenotype consisting of PP, cardiac arrhythmias, facial and skeletal malformations. The disease was first discovered by Ellen Andersen in 1971 but it has been clinically characterized later on by Al Rabi Tawil (Andersen et al., 1971; Tawil et al., 1994). Paralysis may occur with either hyperkalemia or hypokalemia that exacerbates cardiac arrhythmia. Heart manifestations include ventricular arrhythmia (84% of individuals), long QT syndrome (50% of individuals), abnormal TU wave patterns (73%), and sudden cardiac arrest (10% of individuals). A bidirectional ventricular tachycardia (BVT) is a characteristic rhythm disturbance present only in AS, digitalis intoxication, and ryanodine receptor mutations (Morita et al., 2007).

Keveyis (dichlorphenamide)

Summary of Evidence for Keveyis (dichlorphenamide)

Data was analyzed from a 9-week Phase III, randomized, double-blind, placebo (PBO)-controlled phase and a 52-week open-label extension phase. Adults in the HYP/HOP trial were randomly assigned to receive DCP (current DCP dose if taking DCP before study start or DCP 50 mg twice daily; individuals receiving ACZ before study start were assigned a DCP dose equivalent to 20% of the ACZ dose) or PBO for 9 weeks during the double-blind phase, followed by a 52-week open-label phase.

63 individuals were included in the ITT population (DCP/DCP, n=36; PBO/DCP, n=27). 2 of 65 individuals in the PBO group discontinued from study before the open-label extension phase. The majority of the 63 individuals were male (61.9%), white (84.1%), and had hypokalemic periodic paralysis (68.3%). 47 individuals (74.6%) completed 61 weeks of treatment (study

completer population). For individuals in the study completer population, the median weekly attack rate and median severity-weighted attack rate improved significantly from baseline to Week 61 in both treatment groups. Between-group differences in median weekly attack rates and median severity-weighted weekly attack rates were not significant for changes from baseline at Week 61.

Background on Long-Chain Fatty Acid Oxidation Disorders (LC-FAOD)

LC-FAODs are inherited defects in one of the transport or catalytic enzymes in the mitochondrial LC fatty acid beta oxidation pathway. Collectively, the incidence of FAOD is approximately 1:9,000 births. In the US, prevalence is estimated at about 1:17,000. These enzymatic deficiencies result in partial or incomplete oxidation of fatty acids and accumulation of high concentrations of potentially toxic fatty acid intermediates and an energy deficient state in many organ systems. Typically, presentation is characterized by liver, skeletal muscle, and heart involvement; hypoglycemia/liver dysfunction early in life, muscle weakness/rhabdomyolysis later in life, and episodic cardiomyopathy with or without arrhythmias at any age. Morbidity and mortality are high despite treatment.

Dojolvi (triheptanoin)

Summary of Evidence for Dojolvi (triheptanoin)

Triheptanoin is a medium- (7 carbon) chain triglyceride that bypasses the LC-FAOD enzyme deficiency to provide a source of calories and fatty acids for energy production. The efficacy of triheptanoin for the supplemental treatment of children and adults with LC-FAODs was demonstrated in one fair-to-moderate Phase 2 randomized controlled trial vs. trioctanoin (n=32). This trial showed greater improvement in cardiac mass and function in those receiving triheptanoin over 4 months. Other primary study endpoints, exercise tolerance, total energy expenditure (TEE), and phosphocreatinine recovery after exercise were not significantly different between the treatment groups. However, the study methods employed make these results questionable and clinical relevance is unknown. Evidence from another small fair quality Phase 2 single-arm study, a fair quality single-arm extension study, and a small case series provide supportive evidence.

In the clinical studies available, SAEs requiring hospitalization or acute intervention occurred in up to 55% individuals. These were mostly related to viral infections or rhabdomyolysis and not

related to study treatment. The most common AEs are GI-related, including diarrhea, abdominal pain, and vomiting. GI-related AEs led to dose reduction in up to 35% individuals.

Background on POMC, PCSK1, or LEPR Deficiency

Obesity associated with variants in genes involved in the leptin/melanocortin pathway or hypothalamic melanocortin-4 receptor (MC4R) pathway accounts for 5% of severe early-onset obesity. An estimated 12,800 individuals in the US have a homozygous or compound heterozygous genetic mutation in the MC4R pathway. Affected individuals with variants in the MC4R pathway are of normal weight at birth but quickly gain excessive weight. Symptoms include constant hunger, hyperphagia, and obesity. Children often hoard food, eat in secret, and fight others for food. Lifestyle modification and bariatric surgery are often ineffective in causing weight loss.

Imcivree (setmelanotide)

Summary of Evidence for Imcivree (setmelanotide)

Setmelanotide has been studied in two identical, unpublished, Phase 3 trials in a total of 21 individuals with proopiomelanocortin (POMC) or leptin receptor (LEPR) deficiency obesity. In both trials, setmelanotide met the primary endpoint of proportion of individuals with ≥10% weight loss compared to baseline at ~52 weeks (POMC: 80%, p<0.0001; LEPR: 45%, p=0.0001). Mean weight loss was 31.9 kg (-25.4% of baseline [BL] body weight) and 16.7 kg (-12.5% of body weight from BL), respectively. Mean change in body mass index (BMI) in individuals ≥19 years of age was -22.3% in the POMC trial and -10.6% in the LEPR trial; mean change in BMI in individuals <19 years was -49.2% and -13.35%, respectively. Hunger score (rated on a 0–10-point Likert scale) decreased by 2.7 and 2.2 points from BL to the study endpoint with the LEPR and POMC trials, respectively.

Setmelanotide was also studied in two Phase 2 trials in individuals with LEPR and POMC deficiency obesity which consisted of five case reports rather than controlled trials. All reports supported the efficacy of setmelanotide with weight loss of -11.4% to -23.9% of body weight over 13-42 weeks. In addition, a long-term trial extension conducted in nine individuals found weight loss and decreased hunger scores were maintained to 89 weeks with setmelanotide and that 56% of individuals continued to lose weight during the trial extension.

The efficacy of Imcivree for weight reduction in adults and pediatric individuals aged 4 years and older with acquired HO was assessed in a randomized, double-blinded, placebo-controlled 56- to 60-week clinical trial [Trial 1 (NCT05774756)]. The trial enrolled individuals 4 years and older with acquired HO due to hypothalamic injury or dysfunction. Adult individuals had a BMI of ≥30 kg/m2 and pediatric individuals had a BMI ≥95th percentile for age and sex. In Trial 1, eligible individuals were randomized to either setmelanotide or placebo and entered an up to 8-week dose titration period followed by a 52-week treatment period. Efficacy analyses were conducted for 142 individuals. The proportion of individuals who discontinued trial drug in Trial 1 were 10.6% of the Imcivree treated group and 12.5% of the placebo-treated group. The primary efficacy parameter was mean percent change in BMI from baseline after 52 weeks on a therapeutic regimen of setmelanotide compared to placebo. Individuals who received Imcivree achieved a −15.8% reduction in BMI compared with a +2.6% increase in BMI in individuals who received placebo at 52 weeks (P <0.0001).

Common adverse events (AEs) in Phase 3 trials were injection site reactions (100%), hyperpigmentation of skin (73%-100%), and nausea ± vomiting (45%-100%). Little information about the severity or time course of these AEs was reported. While no increase in depression was seen, suicidal ideation or behavior was noted in six of 21 individuals, four of which were on treatment.

Background on Primary Hypoxaluria Type 1

Primary hyperoxaluria (PH) type 1 is a rare, autosomal recessive inborn error of glyoxylate metabolism characterized by the overproduction of oxalate, which is poorly soluble and is deposited as calcium oxalate in various organs. In PH type 1, the genetic defect results in decreased or absent activity of the hepatic peroxisomal enzyme alanine: glyoxylate aminotransferase (AGT), which normally converts glyoxylate to glycine, which leads to an increase in the glyoxylate pool and later overproduction of oxalate. The increased urinary excretion of oxalate results in urinary calcium oxalate supersaturation, which leads to crystal aggregation, urolithiasis, and/or nephrocalcinosis. As oxalate is primarily excreted in the urine, the kidney is the prime target for oxalate deposition, which leads to end-stage kidney disease in a significant number of cases.

Oxlumo (lumasiran)

Summary of Evidence for Oxlumo (lumasiran)

The efficacy and safety of Oxlumo (lumasiran) for the treatment of primary hyperoxaluria type 1 (PHI) to lower urinary oxalate level were studied in two clinical trials, ILLUMINATE A and ILLUMINATE B. ILLUMINATE-A was a randomized, double-blind trial comparing lumasiran and placebo in 39 individuals 6 years of age and older with PH1 and an eGFR ≥30 mL/min/1.73 m^2. The primary endpoint was the percent reduction from baseline in 24-hour urinary oxalate excretion corrected for BSA averaged over Months 3 through 6. The mean percent change from baseline in 24-hour urinary oxalate in the Oxlumo group was -65% (95% CI: -71, -59) compared with -12% (95% CI: -20, -4) in the placebo group, resulting in a between-group mean difference of 53% (95% CI: 45, 62; p<0.0001). By Month 6, 52% (95% CI: 31, 72) of individuals treated with Oxlumo achieved a normal 24-hour urinary oxalate corrected for BSA (≤0.514 mmol/24 hr/1.73 m2) compared to 0% (95% CI: 0, 25) placebo-treated individuals (p=0.001). ILLUMINATE-B was a single-arm study in 18 individuals <6 years of age with PH1 and an eGFR >45 mL/min/1.73 m2 for individuals ≥12 months of age or a normal serum creatinine for individuals <12 months of age. Efficacy analyses included the first 16 individuals who received 6 months of treatment with Oxlumo. The primary endpoint was the percent reduction from baseline in spot urinary oxalate: creatinine ratio averaged over Months 3 through 6. Individuals treated with Oxlumo achieved a reduction in spot urinary oxalate: creatinine ratio from baseline of 71% (95% CI: 65, 77).

The efficacy and safety of Oxlumo (lumasiran) for the treatment of primary hyperoxaluria type 1 (PHI) to lower plasma oxalate level were studied in one clinical trial, ILLUMINATE C. ILLUMINATE-C was a multicenter study, single-arm trial that enrolled 21 individuals aged 12 months of age or older with PH1 and eGFR $\leq$ 45 ml/min/1.73 m^2 or individuals less than 12 months of age with an elevated serum creatinine, including individuals on hemodialysis. The study consisted of two cohorts: Cohort A and Cohort B. Cohort A included 6 individuals, who did not require the dialysis. Cohort B included 15 individuals, who were on stable regimen of hemodialysis. The primary endpoints for each cohort were as follows: the percent change in plasma oxalate from baseline to month 6 for Cohort A and the percent change in pre-dialysis plasma oxalate from baseline to month 6 for Cohort B. At month 6, the least square mean percent change in plasma oxalate for Cohort A was - 33%, while the least square mean percent change in pre-dialysis plasma oxalate for cohort B was - 42%.

Rivfloza (nedosiran)

Summary of Evidence for Rivfloza (nedosiran)

Rivfloza is an RNAi agent designed to inhibit expression of hepatic lactate dehydrogenase (LDH), the enzyme thought responsible for the terminal step of oxalate synthesis. PHYOX2 was a randomized, double-blind, Phase 2 trial comparing Rivfloza and placebo in individuals 6 years of age or older with PH1 or PH2 and an eGFR ≥30 mL/min/1.73 m2. Individuals received monthly doses of Rivfloza (n = 23) or placebo (n = 12). The primary efficacy endpoint was the area under the curve, from Days 90 to 180, of the percent change from baseline in 24-hour urinary oxalate excretion (AUC24-hour Uox). The least-squares (LS) mean AUC24-hour Uox was -3486 (95% CI: -5025, -1947) in the Rivfloza group compared to 1490 (95% CI: 781, 3761) in the placebo group, for a between group difference of 4976 (95% CI: 2803, 7149; p< 18 years of age) averaged over Days 90, 120, 150 and 180, was -37% (95% CI: -53%, -21%) in the Rivfloza group and 12% (95% CI: -12%, 36%) in the placebo group, for a between group difference of 49% (95% CI: 26%, 72%). Among individuals with PH1, the between group difference was 56% (95% CI: 33%, 80%). After 6 months of treatment in PHYOX2, study participants could enroll in an ongoing single-arm extension study, PHYOX3 (NCT04042402), in which all individuals were treated with Rivfloza. The reduction in urinary oxalate was maintained in the 13 individuals with PH1 who received an additional 6 months of treatment in PHYOX3. In the PHYOX2 trial, 18 individuals with PH1 received Rivfloza and 11 individuals received placebo. Of the 18 individuals treated with Rivfloza, 17 individuals received ≥5 months of active treatment. The most common adverse reaction was injection site reactions, which were reported in seven individuals with PH1 (39%) on Rivfloza as compared to no individuals on placebo. Injection site reactions included erythema, pain, bruising, and rash and were generally mild and did not lead to discontinuation of treatment.

Background on MoCD Type A

Molybdenum cofactor deficiency (MoCD) is an autosomal recessive disorder that results from one of several single gene defects in the biosynthetic pathway of molybdenum cofactor. Approximately two-thirds of individuals have MoCD type A, in which mutations in molybdenum cofactor synthesis gene 1 (MOSC1) result in the inability to synthesize the first intermediate in the pathway, cyclic pyranopterin monophosphate (cPMP), and the toxic accumulation of sulfites in blood and urine. Most individuals present during the first few days of life with exaggerated startle, lethargy, intractable seizures, and autonomic dysfunction, a complex of symptoms that may resemble hypoxic ischemic encephalopathy. The disorder can be diagnosed by urine

dipsticks showing elevated sulfite levels and confirmed with urinary cPMP testing and mutational analysis.

Nulibry (fosdenopterin)

Summary of Evidence for Nulibry (fosdenopterin)

The efficacy of Nulibry and rcPMP were assessed in a combined analysis of the 13 individuals with genetically confirmed MoCD Type A from Study 1 (n=8), Study 2 (n=1), and Study 3 (n=4) who received substrate replacement therapy with Nulibry or rcPMP. Efficacy was assessed by comparing overall survival in pediatric individuals treated with Nulibry or rcPMP (n=13) with an untreated natural history cohort of pediatric individuals with genetically confirmed MoCD Type A who were genotype-matched to the treated individuals (n=18). Survival at 1 year was 92% (95% CI, 57-99%) for the Nulibry or rcPMP group and 67% (CI, 40-83%) for the genotype-matched, historical control group. Survival at three years was 84% (CI, 49-96%) for the Nulibry and rcPMP group compared with 55% (CI, 30-74%) for the genotype-matched historical control group. Mean survival time at 1 year was 11 months (CI, 9-13) for the treatment group and 10 months (CI, 8-12) for the control arm. At 3 years, the mean survival time for individuals treated with Nulibry or rcPMP was 32 months (CI, 26-37) and 24 months (CI, 17-31) for the genotype-matched historical control group.

Assessment of adverse reactions for Nulibry is based on data from two open-label, single-arm studies, Study 1 (n=8) and Study 2 (n=1), in individuals with a confirmed diagnosis of MoCD Type A (8 of the 9 individuals were previously treated with rcPMP). In these studies, individuals received a daily intravenous infusion of Nulibry. The median exposure to Nulibry was 4.3 years and ranged from 8 days to 5.6 years. The most common adverse events were catheter-related complications (89%), pyrexia (78%), viral infection (56%), pneumonia (44%), otitis media (44%), vomiting (44%), and cough/sneezing (44%).

Background on Polycythemia Vera

Polycythemia vera (PV) is a rare Philadelphia chromosome-negative myeloproliferative neoplasm. Prevalence of PV in the US is estimated at 44-57/100,000 and is more common in individuals over 60 years of age. PV is characterized by increased red blood cells and this is often accompanied by increased white blood cells and increased platelets. Common signs and symptoms include splenomegaly, fatigue, itching, weight loss, night sweats, and variable lab

abnormalities. Complications include but are not limited to thromboembolic events and transformation to blast phase myelofibrosis or acute myeloid leukemia (AML), both of which have a poor prognosis. *JAK2* V617F mutations account for >90% of cases of PV.

Besremi (ropeginterferon alfa-2b-njft)

Summary of Evidence for Besremi (ropeginterferon alfa-2b-njft)

In the primary PROUD study, a total of 254 adults with early PV were randomized and received ROP SC every 2 weeks (n=127) or HU PO daily (n=127) individually titrated to response. After one year in the PROUD-PV study individuals could then elect to continue in the CONTINUATION-PV extension study. A total of 171 individuals elected to continue therapy in the extension, with the ROP arm continuing randomized treatment (n=95) and the HU arm continuing randomized treatment or switching to best available therapy (BAT; n=76) (excluding ROP). After 12 months therapy in PROUD-PV, complete hematologic response + normal spleen size (primary endpoint) was 21% in the ROP arm and 28% in the HU arm (difference: -6.57; 95% CI -17.23 to 4.09; p=0.23); noninferiority was not demonstrated. However, with longer-term treatment in the CONTINUATION-PV extension study, significantly more individuals achieved complete hematologic response + improvement in disease burden at Month 36 (53% vs. 38%; rate ratio: 1.42; 95% CI 1.01 to 2.00; p=0.044), achieved a complete hematologic response at Month 24 (p=0.011) and Month 36 (p=0.012), and achieved molecular response at Months 24 and 36 (both p≤0.0001). Response kinetics varied between the two treatment groups, with the HU/BAT treatment group reaching maximal response at 6 months and gradually declining thereafter, whereas the ROP treatment group responses increased steadily over the 3-year follow-up. Additionally, mutant JAK2 allele burden began to rebound in the second year of treatment and returned to baseline levels by the third year in the HU/BAT group but decreased further in the second and third years of treatment, to half of baseline level, in the ROP group.

Serious adverse events with ROP included depression (1.1%), atrial fibrillation (1.1%), and acute stress disorder (0.6%). The incidence of major cardiovascular events was 10% in the ROP arm and 6% in the HU/BAT arm and major thrombotic events were similar between the treatments (3% each). The most frequent treatment-related Grade 3/4 adverse events in the ROP arm were increased GGT (6%) and increased ALT (3%) and in the HU/BAT arm were leukopenia (5%) and thrombocytopenia (4%). 2 cases of acute myeloid leukemia occurred in the HU/BAT arm.

Background on Achondroplasia

Achondroplasia (ACH) is one of the most common forms of skeletal dysplasia disorders resulting in short stature (dwarfism). The incidence rate of ACH is estimated to be 1 in 25,000 with an increased incidence rate with advancing paternal age. ACH is caused by a heterozygous, gain-of-function mutation in the fibroblast growth factor receptor 3 (FCFR3) resulting in impaired endochondral ossification and disproportional development of long bones. ACH is associated with several medical and neurologic complications including increased risk of recurrent otitis media, sleep apnea, and spinal stenosis. Children with achondroplasia often experience delayed development and independent self-care skills and need assistance with completion of everyday tasks.

Voxzogo (vosoritide)

Summary of Evidence for Voxzogo (vosoritide)

In a phase III trial, vosoritide demonstrated efficacy in increasing annualized growth velocity and mean Z score for height in children aged 5-18 years of age with achondroplasia and open growth plates after 52 weeks of treatment. Compared to placebo, the vosoritide group had an increased in annualized growth velocity 1.57 cm (95% CI 1.22 to 1.93, p value < 0.0001) and height Z score of 0.28 (0.17 to 0.39, p value < 0.0001) but no statistically significant different change in upper to lower body segment ratio from baseline was observed. In a long-term extension study, vosoritide demonstrated continued efficacy after an additional 52 weeks. In individuals that continued vosoritide, annualized growth velocity was maintained at 5.57 ± 1.10 cm/year compared to 5.67 ± 0.98 cm/year during the previous 52 weeks. Long-term effects on adult height, adult body proportionality, and health/medical complications have yet to be determined at this time.

Vosoritide was generally well tolerated with few serious adverse events and related discontinuations. The most common adverse events were redness and swelling at the injection site, but reactions were considered mild. No anaphylaxis was observed during clinical trials. Endothelial C-type natriuretic peptide plays a role in blood pressure regulation and has vasodilating effects. In a phase III study, blood pressure decrease was reported in 7 individuals (12%) in the vosoritide group compared to 3 (5%) in the placebo group. Hypotensive events were considered transient and resolved without medical intervention. Vosoritide has not been studied in individuals with concurrent antihypertensive therapy or individuals who have a history of symptomatic hypotension.

Background on Friedreich's Ataxia

Friedreich's ataxia, a neurological disorder inherited in an autosomal recessive manner, is caused by the mutations in the frataxin (FXN) gene and is the most prevalent hereditary form of ataxia. Frataxin, a mitochondrial protein, plays a crucial role in biogenesis of iron-sulfur clusters, antioxidation, iron detoxification, and regulation of iron storage. The frataxin gene is expressed at high levels in tissues that are affected by Friedreich's ataxia, such as the brain, heart, and pancreas. The incidence of Friedreich's ataxia is rare, affecting 1 in 50,000 people in the USA. Neurological dysfunction, cardiomyopathy, and diabetes mellitus are the primary clinical manifestations of Friedreich's ataxia. MRI neuroimaging of the brain and spinal cord is suggested to eliminate other potential causes of ataxia. In most cases, the Friedreich ataxia appears in the adolescent years, but individuals as young as 2 years old and as old as 70 years old can also develop it.

Summary of Evidence for Skyclarys (omaveloxolone)

Skyclarys was studied in a 48- week phase 2, randomized, double-blinded, placebo-controlled trial. Overall, 103 individuals aged 16 to 40 years old with confirmed diagnosis of Friedreich's ataxia randomized 1:1 to receive Skyclarys 150mg once daily (n = 51) or placebo once daily (n = 52). The primary objective of the trial was to compare the change in a modified Friedreich's Ataxia Rating Scale (mFARS) score from baseline, which is a clinical assessment tool used to evaluate an individual's function. The score comprises four domains that assess valvular function, upper limb coronation, lower limb coordination, and upright stability, with a maximum score of 99. A lower score indicates less physical impairment. The treatment with Skyclarys resulted in statistically significant mFARS score change (less impairment) compared to placebo. The least square mean changes from baseline at week 48 was -1.56 for the Skyclarys treatment group compared to 0.85 for the placebo group with p value of 0.0138. The secondary objective was to measure the change of peak workload (watts/kg) during exercise testing.

In general, omaveloxolone was well-tolerated. The most frequent adverse reactions reported were headache, nausea, abdominal pain, fatigue, diarrhea, and musculoskeletal pain. Additionally, there was a transient, reversible increase in aminotransferase levels observed in the treatment group, without increasing total bilirubin or other signs of liver injury.

Lamzede (velmanase alfa-tycv)

Background on alpha mannosidosis

Alpha mannosidosis is a consequence of anomalous sugar (called mannose-containing oligosaccharides) accumulations within cells dispersed throughout the body. The fundamental aberration that facilitates this process is an inherent inadequacy of lysosomal alpha-mannosidase enzymes, which are responsible for disintegrating glycoproteins into lesser fragments. Due to the accumulation of mannose-containing oligosaccharides in the lysosomes, these organelles enlarge, resulting in significant impairment of cellular operations. Immune deficiency, facial and skeletal deformities, hearing loss and cognitive disabilities are frequent traits associated with this condition.

Alpha mannosidosis is a genetic disorder that is rare and inherited in an autosomal recessive manner. It is caused by mutations in a gene MAN2B1 location on chromosome 19. Diagnosis of alpha mannosidosis involves measuring acid amino-mannosidase activity in leukocytes or other nucleated cells, such as fibroblasts. Genetic testing can be performed on DNA from peripheral blood cells to identify mutations in the gene.

Alpha mannosidosis treatment includes symptoms management, bone marrow transplant (BMT) and enzyme replacement therapy with Lamzede (velmanase alfa-tycv).

Summary of Evidence for Lamzede (velmanase alfa-tycv)

The safety and efficacy of Lamzede (velmanase alfa-tycv) were assessed in two clinical studies in individuals with alpha mannosidosis. Lamzede is indicated for use in individuals with alpha mannosidosis.

Study 1 was phase 3 randomized, double-blind, placebo-controlled, multi-center, parallel group study consisting of 25 individuals (13 adult individuals and 12 pediatric individuals) with alpha mannosidosis. All individuals but one was treatment naïve with Lamzede. All the individuals had alpha-mannosidase activity below 11% of the normal at the baseline. Individuals were randomized to receive either 1 mg/kg of Lamzede or placebo every week for 52 weeks. The primary efficacy endpoint was the reduction of oligosaccharide in serum and the number of steps climbed in 3-minutes (3MSCT) compared to the baseline. At 12 months, the treatment group exhibited a mean relative reduction in serum oligosaccharide levels from baseline of -75.8% whereas the placebo group demonstrated a mean relative reduction in sugar levels from

baseline of -20.3%. Similarly at 12 months, the treatment group exhibited a mean relative change in 3MSCT from baseline of 0.5% whereas the place group demonstrated a mean relative change in 3MSCT from baseline was -3.6%. The secondary efficacy endpoint was change in 6-min walk test (6MWT) and the force vital capacity (FVC %) of the predicted normal value from the baseline at week 52. The mean relative change in FVC (% predicted) from baseline was 11.4% in the treatment group at 12 months, while the mean relative change in FVC (% predicted) from baseline was 1.9% in the placebo group 12 months. Similarly, the mean relative change in 6MWT from baseline was 1.2% in the treatment group at 12 months, while the mean relative change in 6MWT from baseline was -0.8% in the place group at 12 months. All the individuals completed the trial. Common adverse events include nasopharyngitis, pyrexia, headache and arthralgia. One Lamzede -treated individual experienced acute renal failure.

Study 2 was phase II multicenter, open label study, single arm trial consisting of 5 pediatric individuals below 6 years of age with alpha mannosidosis. All the individuals had alpha mannosidase activity below 10% of the normal at the baseline. Individuals received 1 mg/kg of Lamzede for 24 months. The primary outcome was the safety and tolerability of velmanase alfa and secondary outcome included level of serum oligosaccharide, the peabody developmental motor scale test (PDMS-2), 3-minute stair climb test (3MSCT) and 6-minute walk test (6MWT). The mean percentage changes from baseline for serum oligosaccharides at 24 months was -65.8%. The common adverse effects include cough, otitis media, rhinitis, conjunctivitis, fall, ligament sprain and upper respiratory tract infection. One individual experienced chills and hyperthermia.

Overall, about 36% adult individuals and 58% of pediatric individuals experienced hypersensitivity reactions. More individuals experienced infusion-associated reactions in Lamzede -treated individuals with anti-velmanase alfa-tycv antibodies compared to individuals who were ADA-negative.

Daybue (trofinetide)

Background on Rett syndrome

Rett Syndrome (RTT) is a rare, progressive neurodevelopmental disorder affecting mostly female individuals. Rett syndrome affects about 6000 to 9000 individuals in the United States. Rett syndrome is most likely caused by mutations in the MECP2 gene, which encodes methyl-CpG binding protein 2 (MeCP2). MeCP2 can be found in any tissues, but most likely can be found in the brain. In some individuals with atypical RTT can be caused by mutations in CDKL5 or FOXG1. In the case of MeCP2 mutation, the MeCP2 mutation can lead to failure of synaptic maturation

and maintenance in the cortex. The clinical phenotype of RTT can be divided into two categories: typical (classic) RTT or atypical (variant) RTT. In the typical RTT, the individual develops normally for a brief period and then experience loss of speech and purposeful hand use at 12 to 18 months. Other symptoms include head growth deceleration, seizures, autistic features, and beathing abnormalities. The growth regression is followed by the period of some recovery of nonverbal communication, nonverbal interactions with the environment and improved eye contact. This improvement is followed by gradual deterioration in the gross motor function through adulthood. The individuals also experience onset of stereotypic hand movements and gait abnormalities. The atypical RTT might not have all clinical features of typical RTT. The primary diagnostic criteria for RTT include partial or complete loss of acquired purposeful hand skills and acquired spoken language, gait abnormalities and stereotypic hand movements. The treatment includes the symptoms management, occupational, physical therapy, speech therapy, rehabilitative and behavioral therapy. Daybue is the first drug approved for the Rett syndrome in adults and children 2 years of age and older.

Summary of Evidence for Daybue (trofinetide)

Daybue was studied in randomized, double-blind, placebo-controlled, parallel-group ,12-week phase 3 trial. The goal of the trial was to study Trofinetide for female individuals aged 5-20 years with diagnosis of typical Rett Syndrome based on the Rett Syndrome Diagnostic Criteria with a documentation of mutation in MECP2 gene. Individuals were randomized to receive Trofinetide (n = 93) 30-60 ml based on the subjects' weight at baseline or placebo (n = 94) 30-60 ml based on the subjects' weight at the baseline. The primary efficacy endpoint was to compare Clinical Global Impression-Improvement (CGI-I) Score at week 12 and change in Rett Syndrome Behavior Questionnaire (RSBQ) total score from baseline to week 12. The RSBQ score is a 45-item rating scale completed by the caregiver which evaluates Rett Syndrome symptoms. The lower score implies lesser severity in signs and symptoms of Rett Syndrome. The RSBQ score change in treatment group was -5.1 at week 12 compared to the RSBQ score change in placebo group was -1.7 at week 12 with p value of 0.0175. The CGI-I score is completed by the clinician to evaluate if the individual has improved or worsened on a 7-point scale in which lower score indicates more improvement. The CGI-I score was 3.5 in the treatment group at week 12 compared to the CGI-I score was 3.8 in the placebo group at week 12 with p value of 0.0030.

The secondary endpoints included change in Rett Syndrome Caregiver Burden Inventory (RTT-CBI) total score, Overall Quality of Life Rating of the Impact of Childhood Neurologic Disability Scale (ICND) at week 12, change in Communication and Symbolic Behavior Scales Developmental Profile Infant-Toddler Checklist-Social (CSBS-DP-IT-Social) composite score from

baseline to week 12. The CSBS-DP-IT-Social composite score change was -0.1 in the treatment group at week 12 compared to -1.1 in the placebo group at week 12 with p value of 0.0064.

The common adverse events were diarrhea (80.6% with trofinetide vs 19.1% with placebo) and vomiting (26.9% with trofinetide vs 9.6% with placebo). The study was discontinued in 17.2% individuals in the trofinetide group compared to 2.1% in the placebo group due to treatment emergent adverse events (TEAEs). The most common adverse reaction leading to discontinuation was diarrhea (15%).

Summary of Evidence for Sohonos (palovarotene)

In the phase 3, single arm MOVE study, 107 individuals with fibrodysplasia ossificans progressiva (FOP) aged 4 years and older received palovarotene 5 mg daily with increased dosing at the time of a flare-up. The primary endpoint is the annualized change in new heterotopic ossification volume with untreated individuals from a longitudinal natural history study. The median age (range) of individuals in the palovarotene group was 14 (8, 61) years and 18 (9, 56) years in the untreated group from the natural history study. There were more male than female subjects in both groups. The 18-month interim results showed a 62% reduction in mean annualized new heterotopic ossification volume in individuals treated with palovarotene (8,821 mm^3) (n = 97) vs untreated (23,318 mm^3) (n = 98) individuals, and the post-hoc weighted linear mixed effects (wLME) model yielded a treatment difference of −11,611 mm^3 (nominal P = .0292) in MOVE compared with no treatment.

The findings of MOVE are supported by a fair quality, phase 2, randomized, double-blind, placebo-controlled study in 40 individuals aged 6 years and older. The proportion of responders at week 6 by plain radiograph was 100% with palovarotene 10/5 mg; 88.9% with palovarotene 5/2.5 mg; 88.9% with placebo (P = .17). At week 12, the proportions were 95.0% with palovarotene 10/5 mg; 88.9% with palovarotene 5/2.5 mg; 77.8% with placebo (P = .15). Week 12 least-squares mean (LS mean) new heterotopic ossification volume, assessed by CT, was 3.8 X 10^3 mm^3 with palovarotene 10/5 mg; 1.3 X 10^3 mm3 with palovarotene 5/2.5 mg; 18.0 X 10^3 mm^3 with placebo (pairwise tests vs placebo: P ≤ .12). The higher-than-expected proportion of responders in the placebo group may indicate that 6 weeks was not a long enough period to measure response.

The most frequently reported adverse reactions (occurring in > 20% of individuals) with palovarotene were dry skin (78%), dry lip (55%), pruritus (55%), alopecia (41%), rash (39%), erythema (32%), skin exfoliation (31%), dry eye (26%), skin reaction (24%) and skin abrasion (21%), with most being mild or moderate in severity.

Summary of Evidence for Cystadane (betaine anhydrous)

Betaine anhydrous, a methylating agent, is indicated for the treatment of homocystinuria to decrease elevated homocysteine blood concentrations in adults and pediatric individuals. Homocystinuria is a group of rare, autosomal recessive disorders caused by mutations in specific enzymes that metabolize amino acids. Elevated levels of homocysteine can lead to abnormalities in the central nervous system, eye, skeletal system, and vascular system. Included within the category of homocystinuria are cystathionine beta-synthase deficiency, 5,10-methylenetetrahydrofolate reductase deficiency, and cobalamin cofactor metabolism defect. Clinical and observational studies demonstrated individuals with homocystinuria who received betaine anhydrous had significant reductions in plasma homocysteine or homocysteine concentrations. Additionally, improvement in seizures or behavioral and cognitive functioning were reported for many individuals. Many of these individuals were also taking other therapies such as vitamin B6 (pyridoxine), vitamin B12 (cobalamin), and folate with variable biochemical responses.

Summary of Evidence for Xolremdi (mavorixafor)

The approval of Xolremdi was based on results of the Phase 3 4WHIM clinical trial, a randomized, double-blind, placebo-controlled, 52-week multicenter study that evaluated the efficacy and safety of Xolremdi in 31 participants 12 years of age and older diagnosed with WHIM syndrome. Over a 52-week period, Xolremdi treatment demonstrated increased time above threshold (TAT) (≥500 cells/µL) for absolute neutrophil count (ANC) ($TAT_{ANC)}$ (least squares [LS] mean [standard error (SE)] 15.0 [1.89] hours) versus placebo (2.8 [1.52] hours) and increased TAT (≥1000 cells/µL) for absolute lymphocyte count (ALC) (TAT_{ALC}) (LS mean [SE] 15.8 [1.39] hours) versus placebo (4.6 [1.15] hours). The annualized infection rate was reduced by approximately 60% in Xolremdi-treated individuals (LS mean [SE] 1.7 [0.5]) compared with placebo-treated individuals (LS mean [SE] 4.2 [0.7]). The most common adverse reactions were thrombocytopenia, pityriasis, rash, rhinitis, epistaxis, vomiting, and dizziness.

Summary of Evidence for Yorvipath (palopegteriparatide)

The approval was supported by results from two studies: the Phase 3 PaTHway trial and the Phase 2 PaTH Forward trial, which both demonstrated reductions in disease-specific physical

and cognitive symptoms and quality-of-life improvement. The majority of individuals who received Yorvipath in the trials achieved normalization of serum calcium and independence from conventional therapy. The primary endpoint of the PaTHway trial was the proportion of individuals who achieved all of the following at Week 26: Albumin-corrected serum calcium in the normal range (8.3–10.6 mg/dL), independence from conventional therapy (defined as requiring no active vitamin D and ≤600 mg/day of calcium supplementation, including no use of as-needed doses) since Week 22, no increase in the study drug dose since Week 22, no missing active vitamin D and calcium data since Week 22, and study drug dose of 30 mcg or less once daily during the 26-week treatment period. Overall, 68.9% of individuals who received Yorvipath met the efficacy endpoint at Week 26, compared with 4.8% in the placebo group. The proportion of individuals in the Yorvipath group who met the efficacy endpoint decreased over time to 39.3% at both Week 52 and Week 78 during the open-label extension (OLE) period. The composite endpoint in the published trial results was independence from conventional therapy, with maintenance of normocalcemia without an increase in the study drug dose in the final 4 weeks of the blinded period. At Week 26, 79% of individuals who received Yorvipath achieved the outcome versus 5% of individuals who received placebo (P <0.0001).

Summary of Evidence for Voydeya (danicopan)

The approval of Voydeya was based on results from the pivotal ALPHA trial, which evaluated Voydeya as an add-on therapy to Ultomiris or Soliris in individuals with PNH who experienced clinically significant extravascular hemolysis. Voydeya met the primary endpoint of change in hemoglobin from baseline to Week 12. It also met all key secondary endpoints of the trial, including transfusion avoidance and change in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score.

Summary of Evidence for Aqneursa (levacetylleucine)

Aqneursa is a modified amino acid (N-acetyl-L-leucine; NALL) that uses monocarboxylate transporters to cross the blood-brain barrier and reach the central nervous system. The primary efficacy outcome was a modified version of the Scale for Assessment and Rating of Ataxia (SARA), referred to as the functional SARA (fSARA). The fSARA consists only of the gait, sitting, stance, and speech disturbance domains of the original SARA. Each domain was rescored from 0 to 4, where 0 is the best neurological status and 4 is the worst, with a total score ranging from 0 to 16. The SARA is a clinical scale that measures the severity of neurologic signs and symptoms with internal consistency in individuals with spinocerebellar ataxia. However, it is not validated in

individuals with NPC. On average, participants treated with Aqneursa for 12 weeks showed a better outcome in their fSARA scores compared with treatment with placebo. The estimated mean fSARA total score was 5.1 when individuals were treated with Aqneursa and 5.6 when individuals were treated with placebo. The estimated treatment difference for the fSARA total score was −0.4 (95% confidence interval [CI]: −0.7, −0.2).

Summary of Evidence for Miplyffa (arimoclomol)

Miplyffa is an oral small molecule that crosses the blood-brain barrier. It is intended to increase the transcription of several genes involved in lysosomal function and facilitate the proper folding and maturation of certain mutant NPC proteins. The approval of Miplyffa was based on data from a randomized, double-blind, placebo-controlled 12-month trial. Most participants continued to receive background miglustat throughout the trial. The rescored 4-domain NPC Clinical Severity Scale (R4DNPCCSS) was the primary outcome. In individuals who received Miplyffa in combination with miglustat, a 0.2-point decrease on the R4DNPCCSS was observed compared with an increase of 1.9 points in individuals who received placebo with miglustat. The prescribing information states that there were insufficient data to determine Miplyffa's efficacy without miglustat and Miplyffa is only approved for use in combination with miglustat.

Summary of Evidence for Crenessity (crinecerfont)

Crenessity was evaluated in two Phase 3 studies, CAHtalyst Adult and CAHtalyst Pediatric. The program included 182 adults and 103 children with classic CAH due to 21OHD. Both trials met their primary endpoint, demonstrating that Crenessity enabled significant glucocorticoid dose reductions and decreased androgen levels. A hypersensitivity reaction, including throat tightness, angioedema, and generalized rash, occurred in a subject after 3 days of treatment with Crenessity. In the placebo-controlled clinical study of adults with classic CAH, the incidence of adrenal crisis was 1.6% in subjects treated with Crenessity and 0% in subjects treated with placebo. In the placebo-controlled clinical study of pediatric subjects with classic CAH, there were no events of adrenal crisis.

Summary of Evidence for Vykat XR (diazoxide choline)

Vykat XR was evaluated in four studies of moderate quality which enrolled the same individual cohort. The DESTINY PWS trial was a 13-week, multicenter, double-blind, randomized, placebo-

controlled Phase 3 trial which enrolled 127 individuals ≥4 years of age with Prader-Willi syndrome (PWS) and moderate-severe hyperphagia (hyperphagia questionnaire for clinical trials [HQ-CT] score >13). Individuals were randomized to Vykat XR (3.3-5.8 mg/kg/day) or placebo. The study did not meet its primary endpoint. There was no significant difference in least square (LS) mean change in HQ-CT score at 13 weeks (-5.94 Vykat XR vs -4.27 placebo, p=0.198). Of note, the minimum important difference (MID) for this outcome is 7. Vykat XR significantly improved change in HQ-CT score in the prespecified subgroup of individuals with severe hyperphagia (baseline HQ-CT score >22) (-9.67 vs -4.26, p=0.012). The trial investigators included an exploratory analysis of data collected before the trial was disrupted by Coronavirus disease of 2019 (COVID-19) closures which found change in HQ-CT favored Vykat XR vs placebo (-6.6 vs -3.5, p=0.037); however, the results did not reach clinical significance. Limitations included short trial duration and the impact of COVID-19. The same individuals were offered enrollment in a 52-week open-label extension (OLE) trial with Vykat XR which found the change in HQ-CT was significantly improved compared with baseline at 13, 26, 39, and 52 weeks (p<0.0001 all comparisons). Note, the change in HQ-CT surpassed the MID of seven at the 26-, 39-, and 52-week assessments. The same individuals were later offered enrollment in a 16-week, double-blind, placebo-controlled, randomized withdrawal study in which 77 individuals were randomized to Vykat XR or placebo. The primary endpoint of LS mean change in HQ-CT score at 16 weeks was significantly improved with Vykat XR compared to placebo (2.6 vs 7.6; LS mean treatment difference -5.0, 95% CI -8.1, -1.8; p=0.002). Lastly, individual data from the DESTINY PWS trial and the OLE trial was combined and compared with data from a PWS natural history study using the same inclusion criteria. Of note, the natural history study individuals were older and had lower (less severe) HQ-CT scores than the DESTINY PWS individuals. The primary endpoint of LS mean change in HQ-CT from baseline was significantly decreased with Vykat XR compared to no treatment at 26 and 52 weeks (-8.3 vs -2.4, p<0.001 and -9.3 vs -3.1, p<0.001, respectively).

Summary of Evidence for Ctexli (chenodiol)

Ctexli was evaluated in a randomized, double-blind, placebo controlled, 2-period with 2-treatment crossover trial in individuals ≥16 years of age. Fourteen individuals were enrolled, and 13 individuals were randomized and treated in a crossover withdrawal design to receive either Ctexli 250 mg or placebo orally three times daily for 4 weeks during 2 double-blind treatment periods. The study also included treatment with Ctexli 250 mg three times daily during an 8-week run-in period and an 8-week open label period in between the 2 double blind withdrawal periods. The total duration of study treatment was 24 weeks. Plasma cholestanol and urine 23S-pentol were assessed at multiple time points. For plasma cholestanol, the estimated mean

change from baseline at day 29 was -2.3 µg/mL when individuals continued Ctexli treatment and 6.2 µg/mL when individuals received placebo. The estimated treatment difference was -8.5 µg/mL (95% CI: -13.2, -3.9). For urine 23S-pentol, the estimated mean change from baseline at day 29 was 185 ng/mL when individuals continued Ctexli treatment and 29506 ng/mL when individuals received placebo. The estimated treatment difference was -29321 ng/mL (95% CI: -45701, -12941).

Summary of Evidence for Cablivi (caplacizumab-yhdp)

Cablivi was evaluated for the treatment of adult individuals with acquired thrombotic thrombocytopenic purpura (aTTP) in the randomized, double-blind, placebo controlled trial HERCULES (NCT02553317). A total of 145 individuals with aTTP were enrolled, randomized either to Cablivi or placebo. Both treatment groups received adjunct plasma exchange and immunosuppressive therapy. The mean dose of Cablivi delivered in the trial was 11 mg and median duration of treatment was 35 days. The efficacy of Cablivi was assessed as time to platelet count response. Individuals treated with Cablivi resulted in shorter time to platelet count response compared to placebo. The efficacy and safety of Cablivi in pediatric individuals 12 years of age and older with aTTP was established with supportive evidence from an observational, retrospective chart review and pharmacokinetic/pharmacodynamic modeling and simulation data. The Cablivi treatment groups experienced lower numbers of TTP-related deaths, recurrence of TTP, or at least one treatment-emergent major thromboembolic event during the treatment period.

Zycubo (copper histidinate)

Background on Menkes disease

The ATP7A gene is responsible for copper metabolism. Classic Menkes disease is caused by the mutation or dysfunction of the ATP7A gene, which results in copper deficiency and reduced activity of copper-dependent enzymes. Neurological symptoms seen with Menkes disease typically begin in individuals 6 to 8 weeks of age. These symptoms include seizures, hypotonia, failure to thrive, hair and connective tissue abnormalities. The worldwide prevalence of Menkes disease was estimated to be 1 in 8664 to 1 in 1355,000 live male births in 2020. Untreated individuals with Menkes disease have a life expectancy of about 2 to 3 years of age and there currently is no cure available.

Summary of Evidence for Zycubo (copper histidinate)

The safety and efficacy of Zycubo in pediatric individuals with Menkes disease was evaluated in two open-label, single-arm clinical trials. Individuals treated with Zycubo ranged from age 0.1 to 31.4 months at treatment initiation, and received 3 years of copper histidinate treatment. Data from the treatment cohort were compared to data from an untreated contemporaneous external control cohort to assess the impact of Zycubo on overall survival. Individuals in the cohort treated with Zycubo had a significant improvement in overall survival compared to individuals in the control cohort, with a 78% reduction of death. In the Zycubo treatment cohort, 15 (48%) individuals survived for greater than 6 years, include 7 (23%) individuals who survived for greater than 12 years. The untreated cohort had no individuals survive past 6 years. Serious adverse reactions were reported in 5% or more individuals in the Zycubo-treated individuals, which included pneumonia, dehydration, seizure, respiratory distress, respiratory syncytial virus infection, cardiopulmonary failure, upper respiratory tract infection, respiratory failure, and vomiting.

Forzinity (elamipretide)

Background on Barth syndrome

Barth syndrome is an X-linked inheritance pattern caused by mutations in the *TAZ* gene, affecting 1 in 1,000,000 males worldwide and 130 to 150 individuals in the United states. Mutation in the *TAZ* gene decreased production of a protein called tafazzin, which results in the alteration of mitochondrial membranes and impact organs like the heart and skeletal muscles. Males with Barth syndrome have distinct clinical features, like a round face, a prominent chin, full cheeks, large ears, and deep set eyes. Individuals with Barth syndrome may also present with variable cardiac abnormalities and low blood cell counts that lead to clinical presentations that include exercise intolerance, muscle weakness, debilitating fatigue, heart failure, recurrent infections, and delayed growth. Diagnosis of Barth syndrome typically occurs during infancy or early childhood, using common markers such as increased levels of 3-methylglutaconic acid and 2-ethyl hydracrylic acid in the urine and blood. Cardiomyopathy onset occurs by 12 months of age in most individuals. There is currently no specific treatment for Barth syndrome. The current treatment approach is symptom management for clinical presentations of heart failure, neutropenia, or infection.

Summary of Evidence for Forzinity (elamipretide)

The safety and efficacy of Forzinity in pediatric and adult individuals with Barth syndrome was evaluated in a randomized, double blind, placebo controlled, crossover trial and its 192-week open-label, single-arm extension period. Twelve individuals aged 12 years or older and weighing greater than 30 kg were treated with Forzinity 40 mg daily injected subcutaneously for the initial 12-week randomized trial. Ten individuals continued treatment in the extension period, and eight individuals participated through week 168. The primary endpoints assessed in the initial randomized trial were distance walked during 6-minute walk test and Total Fatigue Score on the Barth syndrome Symptom Assessment. The primary endpoint results showed that Forzinity was not superior to placebo during the first 12 weeks of treatment. The secondary endpoint assessing increase in knee extensor muscle strength was observed for the Forzinity-treated individuals during the extension period.

Kygevvi (doxecitine and doxribtimine)

Background on thymidine kinase 2 deficiency (TK2d)

Thymidine kinase 2 deficiency is a rare autosomal recessive mitochondrial myopathy caused by mutations in the TK2 gene that encodes for thymidine kinase 2. The condition is typically characterized by progressive muscle weakness that eventually develops into dysphagia and respiratory difficulty and failure. Different subtypes of TK2d based on age of symptom onset that have a varying disease course have been proposed. It is estimated 40% of the affected population has an age of symptom onset less than 1 year of age. This is characterized as the most severe type with rapid symptom progression and children typically surviving a few years. An age of onset of 1 to 12 years of age is estimated to affect 40% of the population. This is a slower (intermediate) progressing type with most individuals requiring a wheelchair by 10 years of age and has a life expectancy typically into adolescence. Age of onset of symptoms after 12 years of age is estimated to affect approximately 20% of the population and is characterized as the slowest progressing type. Individuals may need mobility aids, feeding, and ventilator support with most individuals surviving 20-30 years after symptom onset.

The prevalence of TK2d in the US is estimated to be 600 to 2,700 persons. Thymidine kinase 2 is a mitochondrial enzyme encoded by the TK2 gene. Thymidine kinase 2 catalyzes the initial phosphorylation of deoxycitadine and deoxythymidine that are subsequently converted into deoxynucleotide triphosphates required for mtDNA replication and function. Autosomal recessive TK2 mutations cause mitochondrial DNA depletion, deletions, or both.

Summary of Evidence for Kygevvi (doxecitine and doxribtimine)

Kygevvi contains doxecitine and doxribtimine, two exogenous thymidine nucleosides, that are intended for incorporation into skeletal muscle mtDNA to restore its function (energy production) in individuals with TK2d. The Kygevvi approval is supported by safety and efficacy data from one Phase II clinical study, two retrospective chart review studies, and an expanded access use program. These studies included a total of 82 unique individuals treated with Kygevvi or pyrimidine nucleosides with an age of TK2d symptom onset 12 years or younger. Efficacy was assessed by comparing overall survival in these pediatric and adult treated individuals to an external control group of untreated individuals who were matched to treated individuals using age of TK2d symptom onset (≤ 2 years or >2 to ≤ 12 years). A total of 78 matched pairs were identified. The results showed that survival time from treatment start was improved; treatment reduced the overall risk of death from treatment start by approximately 86% (95% CI: 61%, 96%). Of the 78 treated individuals included in the survival analysis, the median age of TK2d symptom onset was 1.5 years (range: 0.01 to 12 years). The median duration of treatment was 4 years (range: 1 day to 12 years) and the median dose received was 762 mg/kg/day (range: 260 to 800 mg/kg/day).

The most common adverse reactions (incidence ≥5%) are diarrhea, abdominal pain (including abdominal pain upper), vomiting, alanine aminotransferase increased (ALT), and aspartate aminotransferase increased (AST).

Aqvesme (mitapivat)

Aqvesme is a pyruvate kinase activator indicated for the treatment of anemia in adults with alpha or beta thalassemia. It is the first drug to be approved for both individual populations. Two pivotal trials were conducted to evaluate its safety and efficacy: ENERGIZE-T in individuals who are transfusion-dependent with either alpha or beta thalassemia and ENERGIZE in individuals who are non–transfusion-dependent with alpha or beta thalassemia.

The efficacy of Aqvesme was evaluated in ENERGIZE-T, a multinational, randomized, double blind, placebo-controlled clinical study (NCT04770779) of 258 adult individuals with transfusion dependent alpha- or beta-thalassemia, defined as having had 6 to 20 RBC units transfused and no longer than a 6-week transfusion-free period during the 24 weeks prior to randomization. Individuals were included if they had a documented diagnosis of thalassemia (beta-thalassemia with or without alpha globin gene mutations, HbE/beta-thalassemia, or alpha-thalassemia/HbH disease). Among the 258 individuals with transfusion-dependent alpha- or beta-thalassemia, 171 individuals were randomized to receive 100 mg of AQVESME twice daily during the 48-week

double-blind period. The primary endpoint—a ≥ 50% reduction from baseline in red blood cell (RBC) units transfused over any consecutive 12-week period with a reduction of at least two units—was achieved by 52 individuals (30.4%) receiving Aqvesme compared with 11 individuals (12.6%) on placebo, yielding an adjusted rate difference of 17.6% (95% CI, 8.0–27.2; p=0.0003). A ≥ 50% reduction from baseline in red blood cell (RBC) units transfused over any consecutive 24-week period was achieved by 23 individuals (13.5%) receiving Aqvesme compared with 2 individuals (2.3%) on placebo, corresponding to an absolute difference of 11.1% (95% CI, 5.1–17.0; p=0.0003).

The efficacy of AQVESME was evaluated in ENERGIZE, a multinational, randomized, double-blind, placebo-controlled clinical study (NCT04770753) of 194 adults with non-transfusion-dependent alpha- or beta-thalassemia, defined as having had no more than 5 RBC units transfused during the 24-week period prior to randomization and no RBC transfusions within 8 weeks prior to informed consent and during the screening period. Individuals were included if they had a documented diagnosis of thalassemia (beta-thalassemia with or without alpha-globin gene mutations, HbE/beta-thalassemia, or alpha thalassemia/HbH disease) and a baseline Hb concentration ≤10 g/dL. Randomization was stratified by baseline Hb concentrations (≤9 g/dL vs 9.1-10 g/dL) and thalassemia genotype (alpha thalassemia/HbH disease vs beta-thalassemia). Among the 194 individuals with non-transfusion-dependent alpha- or beta-thalassemia, 130 individuals were randomized to receive 100 mg of AQVESME twice daily during the 24-week double-blind period. Efficacy was based upon Hb response, defined as a ≥1 g/dL increase in average Hb concentration from Week 12 through Week 24 compared with baseline and a mean change from baseline in fatigue-related symptoms and impacts assessed by a individual-reported outcome instrument, the Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue). Eighty-seven percent of individuals in the AQVESME arm experienced an increase from baseline in average Hb from Weeks 12 through 24. Of the 55 individuals with Hb response in the AQVESME arm, the average increase in Hb was 1.6 g/dL and the median duration of response was 19.6 weeks (range: 4.0 to 23.4+ weeks) during the 24-week double-blind period. Individuals in the AQVESME arm experienced an improvement compared to placebo in the change from baseline to Week 24 for 2 markers of hemolysis (indirect bilirubin [−0.62 mg/dL (95% CI: −0.80, −0.44)] and lactate dehydrogenase [−24.28 U/L (95% CI: −45.40, −3.15)]).

The most common adverse reactions were headache and insomnia. Because of the risk of hepatocellular injury, Aqvesme is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Monitoring of liver laboratory tests (ALT, AST, alkaline phosphatase, and total bilirubin with fractionation) at baseline and every 4 weeks for 24 weeks and then as clinically indicated. Avoid use of Aqvesme in individuals with cirrhosis. Discontinue Aqvesme if hepatic injury is suspected.

Yuviwel (navepegritide)

The effectiveness of Yuviwel has been established in a clinical trial of navepegritide consisting of a randomized, double-blind, placebo-controlled 52-week period, followed by a single-arm 52-week OLE period (Trial 1; NCT05598320). Trial 1 enrolled 84 treatment-naïve pediatric individuals with genetically confirmed achondroplasia. Key exclusion criteria was radiographic evidence of closed epiphysis and a planned bone surgery. 57 individuals received navepegritide 0.1 mg/kg administered subcutaneously once weekly, and 27 received placebo. The mean age at enrollment was 5.7 years (range: 2 to 12). Forty-five individuals (54%) were male, and 39 individuals (46%) were female. Overall, 74 individuals (88%) were White, 8 individuals (10%) were Asian, and 2 individuals (2%) were mixed race. The individuals had a mean baseline CDC-based height Z-score of -5.0 and mean baseline height of 89 cm (range: 64 to 120). The primary efficacy endpoint was annualized growth velocity (AGV) at Week 52. Height Z-scores calculated using reference data from untreated children with achondroplasia (achondroplasia-specific height Z-score) and using reference data from the general population (CDC-based height Z-score) were also evaluated. Treatment with once-weekly navepegritide for 52 weeks resulted in a least-squares mean treatment difference in AGV of 1.5 cm/year and a least-squares mean increase from baseline in achondroplasia-specific height Z-score of 0.3.

Common adverse events (AEs) across both trials with navepegritide were pyrexia (21%-35%), nasopharyngitis (32%), cough (31%), otitis media (25%), and upper respiratory infection (URI) (21%).4,5 No AEs lead to discontinuation. No serious adverse events (SAEs) were considered treatment related and no deaths occurred in either trial. Injection site reactions (ISRs) occurred in 19% of individuals on navepegritide and anti-CNP antibodies occurred in 2.4%-7.5% of individuals.

2019 Update

Reviewed prescribing information for all drugs and updated Lumizyme (alglucosidase alfa) coverage criteria removing the age limitation for coverage. No new evidence was identified that would require changes to other drugs listed in this policy. Added coverage criteria for Cerdelga (eliglustat), Elelyso (taliglucerase alfa), and Xuriden (uridine triacetate).

2020 Update

Reviewed prescribing information for all drugs. No new evidence was identified that required changes to coverage criteria. Added Keveyis (dichlorphenamide) to policy for the treatment of primary hyperkalemic or hypokalemic periodic paralysis.

2021 Update

Reviewed prescribing information for all drugs. Updated criteria for Fabrazyme (agalsidase beta) from 6 years of age and older to 2 years of age and older as expanded age indication was approved by the FDA in March 2021. Updated criteria for Sucraid (sacrosidase) adding genetic testing for diagnosis. A diagnosis through genetic testing for the sucrase-isomaltase (SI) gene is considered a less invasive alternative to biopsy but still provides a result consistent with biopsy.

2022 Update

Reviewed prescribing information for all drugs. Updated Oxbryta coverage criteria to include individuals 4 years and older. Removed Ruzurgi criteria and trial of Ruzurgi before Firdapase approval as Ruzurgi has been removed from the market. Added coverage criteria for Besremi (ropeginterferon alfa-2b-njft) for the treatment of adults with polycythemia vera. Added coverage criteria for Voxzogo (vosoritide) for the treatment of pediatric individuals with achondroplasia. Reviewed evidence for new indication as reported by FDA. Imcivree (setmalanotide) was approved for use in Bardet-Biedl syndrome and obesity (body mass index (BMI) greater than or equal to 30 kg/m^2) based on a 66-week study in which individuals lost an average of 7.9% of their BMI within 52 weeks of treatment. Added coverage to Imcivree (setmelanotide) for individuals with obesity due to Bardet-Biedl syndrome.

2023 Update

Reviewed prescribing information for all drugs. Updated Livmarli criteria to include individuals 3 months or older. Added criteria for Skyclarys for individuals 16 years or older with Friedreich's ataxia. Added criteria for Lamzede for individuals with alpha-mannosidosis. Added criteria for Daybue for individuals 2 years or older with Rett syndrome. Removed from Tepezza reference to "with expertise in TED treatment". Updated Oxlumo (lumasiran) criteria to include lowering of plasma oxalate levels in pediatric and adult individuals. Added quantity limit to Sucraid

(sacrosidase). Added coverage criteria for Elfabrio (pegunigalsidase alfa-iwxj) for adult individuals with Fabry disease. Updated Fabrazyme and Galafold criteria so that Fabrazyme and Galafold is not being used in combination with Elfabrio as well. Added coverage criteria for generic dichlorphenamide for adult individuals with a diagnosis of primary hyperkalemic or hypokalemic periodic paralysis. Added criteria requirement of having trial and failure of generic dichlorphenamide prior brand Keveyis. Added coverage for Bylvay for the treatment of cholestatic pruritus in individuals 12 months of age and older with Alagille Syndrome (ALGS). Updated benefit for Crysvita (burosumab) from medical/pharmacy benefits to medical benefits. Added coverage criteria for Cholbam (cholic acid) for the indication of either bile acid synthesis disorders due to single enzyme defects or for the adjunctive treatment of peroxisomal disorders (PDs) including Zellweger spectrum disorders. Added coverage for Cystadane (betaine anhydrous) and generic betaine anhydrous for the treatment of homocystinuria. Added Yargesa (generic miglustat) to the generic miglustat criteria. Added coverage criteria for Rivfloza (nedosiran) for the treatment of primary hyperoxaluria type 1. Added coverage criteria for Pombiliti (cipaglucosidase alfa-atga) and Opfolda (miglustat) for the treatment of adults with late-onset Pompe disease.

2024 Update

Reviewed prescribing information for all drugs. Removed Adakveo (crizanlizumab-tmca), Endari (L-glutamine), and Oxbryta (voxelotor) from the policy as these treatments were added to medical policy 5.01.640 Pharmacologic Treatment of Sickle Cell Disease. Updated Voxzogo criteria to remove the age requirement and add the following requirements: the individual has open epiphyses or Tanner Stage <4, growth velocity ≥1.5 centimeters in the last 12 months and does not plan to have limb-lengthening surgery. Updated Lamzede (velmanase alfa-tycv) coverage criteria to include the following requirements: diagnosis of alpha-mannosidosis confirmed by bi-allelic pathogenic variants in the *MAN2B1* gene, individual does not have neurological symptoms, individual is able to ambulate without support, individual has not received a hematopoietic stem cell transplant or bone marrow transplant, and the dose is limited to 1 mg/kg weekly. Updated Livmarli (maralixibat) to include coverage criteria for the treatment of certain individuals with progressive familial intrahepatic cholestasis (PFIC). Added coverage criteria for Hemangeol (propranolol) for the treatment of certain individuals with proliferating infantile hemangioma. Added coverage criteria for Xolremdi (mavorixafor) for the treatment of certain individuals with WHIM syndrome. Added coverage criteria for Voydeya (danicopan) for the treatment of certain individuals with paroxysmal nocturnal hemoglobinuria. Updated Livmarli (maralixibat) progressive familial intrahepatic cholestasis (PFIC) coverage criteria age requirement from 5 years or older to 12 months or older. Updated Brineura

(cerliponase alfa) coverage criteria from individuals 3 years of age and older diagnosed with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) to individuals less than 18 years of age diagnosed with CLN2. Added coverage criteria for Yorvipath (palopegteriparatide) for the treatment of certain individuals with hypoparathyroidism. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.

2025 Update

Reviewed prescribing information for all drugs. Policy updated to indicate that Site of Service Medical Necessity criteria does not apply to Alaska fully-insured members pursuant to **Alaska HB 226** (accessed January 3, 2025). Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Added an exception to the site-of-service requirements for certain individuals receiving treatment for cytokine release syndrome (CRS). Updated Imcivree (setmelanotide) coverage criteria age requirement from 6 years to 2 years of age and older. Added coverage criteria for Crenessity (crinecerfont) for the treatment of certain individuals with congenital adrenal hyperplasia. Added coverage criteria for Vykat XR (diazoxide choline extended-release) for the treatment of hyperphagia in individuals with Prader-Willi syndrome. Added coverage criteria for Ctexli (chenodiol) for the treatment of cerebrotendinous xanthomatosis. Updated Rivfloza (nedosiran) criteria for the management of urinary oxalate levels from aged 9 years or older to aged 2 years or older and updated the recommended dosing for individuals aged 2 to 11 years. Updated Nexviazyme The maximum dose prescribed is: 40 mg/kg every 2 weeks for actual body weight less than 30 kg, 20 mg/kg every 2 weeks for actual body weight 30 kg or greater. Added site of service review for Tepezza (teprotumumab-trbw). Clarified that the Site of Service Medical Necessity criteria can apply to injection drugs. Updated Gamifant (emapalumab-lzsg) coverage criteria to include treatment of certain individuals with HLH/MAS. Updated Livmarli (maralixibat) coverage criteria to clarify dose limitations. Updated Ctexli (chenodiol) and Cholbam (cholic acid) coverage criteria to clarify that the treatments will not be used concomitantly.

2026 Update

Reviewed prescribing information for all drugs. Added Barth Syndrome and Menkes Disease to the list of rare diseases with coverage criteria in this policy. Added coverage criteria for Zycubo (copper histidinate) for the treatment of Menkes disease in pediatric individuals. Added Background on Menkes disease and Summary of Evidence for Zycubo. Added coverage criteria for Forzinity (elamipretide) when used to improve muscle strength in adult and pediatric

individuals with Barth syndrome. Added Background on Barth syndrome and Summary of Evidence for Forzinity. Added Zycubo and Forzinity to the pharmacy benefit application. Updated Cablivi (caplacizumab-yhdp) coverage criteria to reflect its change in indication to include individuals age 12 years and older. Updated the Summary of Evidence for Cablivi to include trial information used for its FDA approval in pediatric individuals. Updated Daybue (trofinetide) coverage criteria to clarify that the initial approval duration is 6 months and the re-authorization duration is 12 months. Added Daybue Stix (trofinetide) to the same coverage criteria as Daybue. Updated Livmarli (maralixibat) coverage criteria to clarify its indication excludes individuals with a subgroup of PFIC type 2 with specific ABCB11 variants resulting in nonfunctional or complete absence of bile salt export pump (BSEP) protein. Updated Livmarli coverage criteria to align with prescribing information dosage and quantity limits for its respective indications for Alagille syndrome (ALGS) and progressive intrahepatic cholestasis (PFIC). Updated Cholbam (cholic acid) coverage criteria to remove the 1200 mg per day dose limit. Updated Oxlumo (lumasiran) coverage criteria to include documentation of liver biopsy demonstrating alanine glycosylate aminotransferase (AGT) deficiency and a mutation in the AGT gene as acceptable forms of diagnosis confirmation. Updated Oxlumo coverage criteria to remove the exclusion of individuals with kidney transplant and clarified that an elevated plasma oxalate (POx) level can be documented as at least 20 µmol/L or 1.76 mg/L. Updated Givlaari (givosiran) re-authorization criteria to clarify that a positive clinical response to therapy is documented with urinary or plasma aminolaevulinic acid (ALA) or porphobilinogen (PBG) levels that has not increased from baseline.

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Appendix

Table 1: Pediatric reference ranges for creatine kinase.[24]

Age	Male	Female
0-90 days	28-300 U/L	42-470 U/L
3-12 months	24-170 U/L	26-240 U/L
13-24 months	27-160 U/L	24-175 U/L
2-10 years	30-150 U/L	24-175 U/L
11-14 years	30-150 U/L	30-170 U/L
15-18 years	33-145 U/L	27-140 U/L

History

Date	Comments
03/01/18	New policy, approved February 13, 2018, effective June 1, 2018. Add to Prescription Drug section. The drugs addressed in this policy may be considered medically necessary when criteria are met, subject to review for Site of Service.
08/01/18	Interim Review, approved July 10, 2018. Added criteria for Crysvita (burosemab). Criteria reviewed by the P&T Committee May 30, 2018.
09/21/18	Minor update. Added Consideration of Age section.
11/01/18	Minor update, the Site of Service criteria was updated for clarity.
01/01/19	Coding update, added new HCPCS code J0584 (new code effective 1/1/19).
02/01/19	Interim Review, approved January 8, 2019. Added criteria for Galafold (migalastat) , Revcovi (elapegademase-lvlr) and Firdapse (amifampridine). Galafold criteria reviewed by the P&T Committee August 28, 2018. Revcovi and Firdapse criteria reviewed by the P&T Committee November 27, 2018.
08/01/19	Interim Review, approved July 9, 2019. Added criteria for Ruzurgi (amifampridine) and Cablivi (caplacizumab-yhdp). Updated criteria for Firdapse (amifampridine).
10/01/19	Annual Review, approved September 10, 2019, effective January 3, 2020. Updated Lumizyme (alglucosidase alfa) coverage criteria. Added criteria for Cerdelga (eliglustat), Elelyso (taliglucerase alfa) and Xuriden (uridine triacetate). Added HCPCS code J3060.

Date	Comments
02/01/20	Interim Review, approved January 14, 2020. Added coverage criteria for generic miglustat and Zavesca for Type 1 Gaucher's disease to mirror RCCV policy.
03/01/20	Interim Review, approved February 11, 2020. Added criteria for Tepezza (teprotumumab-trbw). Added testing to confirm diagnose of Type I Gaucher's disease. Added HCPCS code J3590 to report Tepezza.
04/01/20	Interim Review, approved March 23, 2020. Added Oxbryta (voxelotor) and Adakveo (crizanlizumab-tmca) for the treatment of sickle cell disease. Added Givlaari (givosiran) for the treatment of acute hepatic porphyria. Added Gattex (teduglutide) for the treatment of short bowel syndrome. Added HCPCS codes C9053 and C9056.
07/01/20	Interim Review, approved June 9, 2020. Added Endari (L-glutamine) for the treatment of sickle cell disease. Updated Crysvita (burosumab) criteria to include reference to osteomalacia for radiographic evidence. Removed HCPCS code C9053 and added HCPCS code J0791 for Adakveo. Removed HCPCS code C9056 and added HCPCS code J0223 for Givlaari.
08/01/20	Interim Review, approved July 14, 2020. Updated Tepezza (teprotumumab-trbw) criteria for diagnosis of TED, documented CAS, attestation for patients of reproductive potential, and provider specialty. Added new indication to Crysvita (burosumab) for the treatment of FGF23-related hypophosphatemia in TIO.
11/01/20	Annual Review, approved October 13, 2020. Added Keveyis (dichlorphenamide) for the treatment of primary periodic paralysis. Added HCPCS code J3241 for Tepezza.
12/01/20	Interim Review, approved November 10, 2020. Added Dojolvi (triheptanoin) for the treatment of LC-FAOD.
01/01/21	Interim Review, approved December 8, 2020. Added Sucraid (sacrosidase) for the treatment of genetically determined sucrase deficiency.
02/01/21	Interim Review, approved January 12, 2021. Added Zokinvy (lonafarnib) for the treatment of HGPS and progeroid laminopathies. Added Oxlumo (lumasiran) for the treatment of primary hyperoxaluria type 1. Added HCPCS code J3590.
03/01/21	Interim Review, approved February 9, 2021. Added Imcivree (setmelanotide) for the treatment of chronic weight management due to POMC, PCSK1, or LEPR deficiency. Updated Ruzurgi (amifampridine) criteria removing age limitation. Updated Firdapse (amifampridine) coverage criteria removing age limitation and adding requirement to try Ruzurgi (amifampridine) first.
05/01/21	Annual Review, approved April 22, 2021. Updated criteria for Fabrazyme (agalsidase beta) to 2 years of age and older. Updated criteria for Sucraid (sacrosidase) adding genetic testing for diagnosis and changing to low sucrose diet.
06/01/21	Interim Review, approved May 11, 2021. Added Gamifant (emapalumab-lzsg) for the treatment of primary hemophagocytic lymphohistiocytosis (HLH). Added Aldurazyme (laronidase) for the treatment of MPS I. Added Naglazyme (galsulfase) for the treatment of MPS VI. Added Brineura (cerliponase alfa) for the treatment of late infantile neuronal CLN2. Added Sylvant (siltuximab) for the treatment of multicentric

Date	Comments
	Castleman's disease (MCD). Added Kanuma (sebelipase alfa) for the treatment of lysosomal acid lipase deficiency. Coverage criteria for Gamifant, Aldurazyme, Naglazyme, Brineura, Sylvant, and Kanuma become effective for dates of service on or after September 3, 2021, following 90-day provider notification. Added HCPCS codes J0567, J1458, J1931, J2840, J2860, and J9210.
07/01/21	Coding update, Termed HCPCS code C9074 and added J0224.
11/01/21	Interim Review, approved October 12, 2021. Added criteria for Nulibry (fosdeopterin) for the treatment of MoCD Type A. Added criteria for Nexviazyme (avalglucosidase alfa-ngpt) for the treatment of late-onset Pompe disease. Added criteria for Ryplazim (plasminogen, human-tvmh) for the treatment of PLGD type 1. Added criteria for Bylvay (odevixibat) for the treatment of pruritus in patients with PFIC. Added criteria for Livmarli (maralixibat) for the treatment of pruritus in patients with ALGS. Updated Tepezza (teprotumumab-trbw) criteria to include additional criteria for diagnosis of thyroid eye disease, documentation requirements for thyroid function tests, and the prescriber specialty. Updated Lumizyme (alglucosidase alfa) criteria to include tests that confirm Pompe disease diagnosis and added restriction on concurrent use with Nexviazyme (avalglucosidase alfa-ngpt). Updated Oxlumo (lumasiran) criteria to require that the patient has not received a liver or kidney transplant and to require prescriber specialty. Added site of service review for Adakveo (crizanlizumab-tmca), Aldurazyme (laronidase), and Kanuma (sebelipase alfa) for dates of service on or after February 4, 2022.
01/01/22	Coding update, Added HCPCS code C9085.
04/01/22	Annual Review, approved March 8, 2022. Updated Oxbryta coverage criteria to 4 years and older. Removed Ruzurgi criteria and trial of Ruzurgi before Firdapase approval as Ruzurgi has been removed from the market. Added coverage criteria for Besremi (ropeginterferon alfa-2b-njft) for the treatment of adults with polycythemia vera. Added coverage criteria for Voxzogo (vosoritide) for the treatment of pediatric individuals with achondroplasia. Added Besremi and Voxzogo) to CPT J3590. Added new HCPC codes J0219 and C9090. Added term date to HCPC code C9085.
05/01/22	Interim Review, approved April 12, 2022. Added coverage criteria for Enjaymo (sutimlimab-jome) to decrease the need for RBC transfusion due to hemolysis in adults with CAD. Added coverage criteria for Pyrukynd (mitapivat) for the treatment of hemolytic anemia in adults with PKD. Updated Voxzogo (vosoritide) criteria to document the dose prescribed is appropriate based on the patient's actual body weight. Updated Tepezza (teprotumumab-trbw) criteria to require administration within 9 months of ocular symptom onset, trial of glucocorticoids first, prescribed by an endocrinologist or ophthalmologist with expertise in TED treatment, and that Tepezza is not being used in combination with another biologic immunomodulator. Changes for Tepezza become effective for dates of service on or after August 5, 2022. Added site of service review for Nexviazyme (avalglucosidase alfa-ngpt) for dates of service on or after August 5, 2022.

Date	Comments
06/01/22	Interim Review, approved May 23, 2022. Updated Oxlumo (lumasiran) criteria to include for patients ≤ 5 years of age, an elevated urinary oxalate (UOx) excretion as measured by a spot UOx to creatinine ratio that is above the age-specific upper limit of normal (ULN).
07/01/22	Coding update. Added HCPCS codes C9094 and J2998. Removed HCPCS code C9074.
10/01/22	Interim Review, approved September 13, 2022. Added coverage to Imcivree (setmelanotide) for individuals with obesity due to Bardet-Biedl syndrome. Updated Adakveo (crizanlizumab-tmca) criteria removing requirement the individual has not received blood transfusion therapy within the prior six weeks. Added HCPCS code J1302. Changed the wording from "patient" to "individual" throughout the policy for standardization.
12/01/22	Interim Review, approved November 8, 2022. Added coverage for Xenpozyme (olipudase alfa-rpcp) for the treatment of non–central nervous system manifestations of acid sphingomyelinase deficiency (ASMD). Added a dosage limit to Lumizyme (alglucosidase alfa) effective for dates of service on or after March 1, 2023, following 90-day provider notification. Added coverage criteria for Mepsevii (vestronidase alfa-vjbk) for the treatment of MPS VII effective for dates of service on or after March 1, 2023, following 90-day provider notification. Added site of service review for Mepsevii and Naglazyme (galsulfase) effective for dates of service on or after March 1, 2023, following 90-day provider notification. Added Xenpozyme to HCPC J3590. Added HCPC code J3397 for Mepsevii.
03/01/23	Interim Review, approved February 14, 2023. Updated Enjaymo (sutimlimab-jome) criteria removing the requirement the patient has had one documented RBC transfusion within the past 6 months and removed from re-auth criteria the requirement for reduction in RBC transfusions from baseline. Updated criteria for Fabrazyme (agalsidase beta) and Galafold (migalastat) to include requirement the medications are not being used concurrently. Removed from Xenpozyme (olipudase alfa-rpcp) reference to NPD C along with the genes NPC1 and NPC2.
04/01/23	Coding update. New HCPCS code J0218 added. Effective dates removed from HCPCS code C9090 and J0219. Removed HCPCS code C9085. Removed Xenpozyme name from HCPC code J3590.
05/01/23	Annual Review, approved April 11, 2023. Updated Livmarli criteria to include individuals 3 months or older. Added criteria for Skyclarys for individuals 16 years or older with Friedreich's ataxia. Added criteria for Lamzede for individuals with alpha-mannosidosis. Added criteria for Daybue for individuals 2 years or older with Rett syndrome. Removed from Tepezza reference to "with expertise in TED treatment". Updated Oxlumo (lumasiran) criteria to include lowering of plasma oxalate levels in pediatric and adult individuals. Added quantity limit to Sucraid criteria. Added Lamzedeto HCPC code J3590.
07/01/23	Interim Review, approved June 13, 2023. Added coverage criteria for Elfabrio (pegunigalsidase alfa-iwxj) for adult individuals with Fabry disease. Updated

Date	Comments
	Fabrazyme and Galafold criteria so that Fabrazyme and Galafold is not being used in combination with Elfabrio as well. Added coverage criteria for generic dichlorphenamide for adult individuals with a diagnosis of primary hyperkalemic or hypokalemic periodic paralysis. Added criteria requirement of having trial and failure of generic dichlorphenamide prior brand Keveyis.
09/01/23	Interim Review, approved August 8, 2023. Added coverage for Bylvay for the treatment of cholestatic pruritus in individuals 12 months of age and older with Alagille Syndrome (ALGS).
10/01/23	Interim Review, approved September 12, 2023. Updated benefit for Crysvita (burosumab) from medical/pharmacy benefits to medical benefits. Added coverage criteria for Cholbam (cholic acid) for the indication of either bile acid synthesis disorders due to single enzyme defects or for the adjunctive treatment of peroxisomal disorders (PDs) including Zellweger spectrum disorders.
11/01/23	Interim Review, approved October 10, 2023. Added coverage for Sohonos (palovarotene) for the reduction in the volume of new heterotopic ossification in adults and children with fibrodysplasia ossificans progressiva.
12/01/23	Interim Review, approved November 14, 2023. Added coverage for Cystadane (betaine anhydrous) and generic betaine anhydrous for the treatment of homocystinuria. Added Yargesa (generic miglustat) to the generic miglustat criteria.
01/01/24	Interim Review, approved December 12, 2023. Added coverage criteria for Rivfloza (nedosiran) for the treatment of primary hyperoxaluria type 1. Added coverage criteria for Pombiliti (cipaglucosidase alfa-atga) and Opfolda (miglustat) for the treatment of adults with late-onset Pompe disease. C9094 removed from policy. Code termed 09/2022, and added new HCPCS codes J0217 and J2508.
02/01/24	Annual Review, approved January 22, 2024. Removed Adakveo (crizanlizumab-tmca), Endari (L-glutamine), and Oxbryta (voxelotor) from the policy as these treatments were added to medical policy 5.01.640 Pharmacologic Treatment of Sickle Cell Disease. HCPCS code J0791 removed from policy and moved to new policy 5.01.640.
03/01/24	Interim Review, approved February 13, 2024. Updated Voxzogo criteria to remove the age requirement and add the following requirements: the individual has open epiphyses or Tanner Stage <4, growth velocity ≥1.5 centimeters in the last 12 months and does not plan to have limb-lengthening surgery.
04/01/24	Coding update. Added new HCPCS codes G0138, J1202 and J1203.
05/01/24	Interim Review, approved April 9, 2024. Updated Lamzede (velmanase alfa-tycv) coverage criteria to include the following requirements: diagnosis of alpha-mannosidosis confirmed by bi-allelic pathogenic variants in the MAN2B1 gene, individual does not have neurological symptoms, individual is able to ambulate without support, individual has not received a hematopoietic stem cell transplant or bone marrow transplant, and the dose is limited to 1 mg/kg weekly. Updated Livmarli (maralixibat) to include coverage criteria for the treatment of certain individuals with progressive familial intrahepatic cholestasis (PFIC). Added coverage criteria for

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	Hemangeol (propranolol) for the treatment of certain individuals with proliferating infantile hemangioma.
08/01/24	Interim Review, approved July 9, 2024. Added coverage criteria for Xolremdi (mavorixafor) for the treatment of certain individuals with WHIM syndrome. Added coverage criteria for Voydeya (danicopan) for the treatment of certain individuals with paroxysmal nocturnal hemoglobinuria.
11/01/24	Interim Review, approved October 8, 2024. Updated Livmarli (maralixibat) progressive familial intrahepatic cholestasis (PFIC) coverage criteria age requirement from 5 years or older to 12 months or older. Updated Brineura (cerliponase alfa) coverage criteria from individuals 3 years of age and older diagnosed with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) to individuals less than 18 years of age diagnosed with CLN2. Added coverage criteria for Yorvipath (palopegteriparatide) for the treatment of certain individuals with hypoparathyroidism. Removed HCPCS C9090 effective 7/1/2022, see J2998. Removed drug name Nexviazyme from unlisted HCPCS code, J3590. See J0219. Added drug name, Rivfloza, to unlisted HCPCS code J3590.
01/01/25	Interim Review, approved December 10, 2024. Added coverage criteria for Aqneursa (levacetylleucine) and Miplyffa (arimoclomol) for the treatment of neurological manifestations of NPC. Added coverage criteria for generic miglustat, Opfolda (miglustat), Yargesa (generic miglustat), and Zavesca (miglustat) for the treatment of neurological manifestations of NPC when used in combination with Miplyffa (arimoclomol). Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.
02/01/25	Annual Review, approved January 27, 2025. Policy updated to indicate that Site of Service Medical Necessity criteria does not apply to Alaska fully-insured members; only Medical Necessity criteria for the infusion drug applies pursuant to Alaska HB 226 (link added). Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Added an exception to the site-of-service requirements for certain individuals receiving treatment for cytokine release syndrome (CRS).
05/01/25	Interim Review, approved April 8, 2025. Updated Imcivree (setmelanotide) coverage criteria age requirement from 6 years to 2 years of age and older. Added coverage criteria for Crenessity (crinecerfont) for the treatment of certain individuals with congenital adrenal hyperplasia.
07/01/25	Interim Review, approved June 10, 2025. Added coverage criteria for Vykat XR (diazoxide choline extended-release) for the treatment of hyperphagia in individuals with Prader-Willi syndrome. Added coverage criteria for Ctexli (chenodiol) for the treatment of cerebrotendinous xanthomatosis. Updated Rivfloza (nedosiran) criteria for the management of urinary oxalate levels from aged 9 years or older to aged 2 years or older and updated the recommended dosing for individuals aged 2 to 11 years. Updated Nexviazyme The maximum dose prescribed is: 40 mg/kg every 2 weeks for actual body weight less than 30 kg, 20 mg/kg every 2 weeks for actual body weight 30 kg or greater. Added HCPC J3490 for Rivfloza. The following policy changes are

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	effective October 3, 2025, following 90-day provider notification. Added site of service review for Tepezza (teprotumumab-trbw). Clarified that the Site of Service Medical Necessity criteria can apply to injection drugs.
11/01/25	Interim Review, approved October 14, 2025. Updated Gamifant (emapalumab-lzsg) coverage criteria to include treatment of certain individuals with HLH/MAS. Updated Livmarli (maralixibat) coverage criteria to clarify dose limitations. Updated Ctexli (chenodiol) and Cholbam (cholic acid) coverage criteria to clarify that the treatments will not be used concomitantly.
01/01/26	Interim Review, approved December 22, 2025. Updated Lumizyme (alglucosidase alfa), Nexviazyme (avalglucosidase alfa-ngpt), and Pombiliti (cipaglucosidase alfa-atga) to preferred products. Updated generic dichlorphenamide coverage criteria to include a quantity limit. Added Ormalvi (dichlorphenamide) to generic dichlorphenamide coverage criteria for the treatment of primary hyperkalemic or hypokalemic periodic paralysis. Updated Keveyis (dichlorphenamide) quantity limit and added Ormalvi (dichlorphenamide) as a preferred alternative treatment.
03/01/26	Annual Review, approved February 10, 2026. Added coverage criteria for Zycubo (copper histidinate) for the treatment of Menkes. Added coverage criteria for Forzinity (elamipretide) when used to improve muscle strength with Barth syndrome. Updated Cablivi (caplacizumab-yhdp) coverage criteria from 18 years and older to 12 years and older. Updated Daybue (trofinetide) coverage criteria to clarify approval durations. Added Daybue Stix (trofinetide) to the same coverage criteria as Daybue. Updated Livmarli (maralixibat) coverage criteria to exclude individuals with a subgroup of PFIC type 2 and to clarify its quantity limits. Updated Cholbam (cholic acid) coverage criteria to remove the dose limit. Updated Oxlumo (lumasiran) coverage criteria to clarify lab requirements for diagnosis confirmation and remove the exclusion of kidney transplant. Updated Givlaari (galoisian) re-authorization criteria to clarify documentation requirements. Added HCPCS J1809 for Nulibry.
04/01/26	Interim Review, approved March 10, 2026. Added coverage criteria for Kygevvi (doxecitine and doxribtimine) for treatment of thymidine kinase 2 deficiency. Added coverage criteria for Aqvesme (mitapivat) for treatment of alpha- or beta-thalassemia. Updated criteria of Cerezyme (imiglucerase) to include treatment of Type 3 Gaucher's disease, and removed age requirement. The following policy changes are effective July 2, 2026, following 90-day provider notification. Added site of service review for Givlaari (givosiran).
09/01/26	Interim Review, approved August 11, 2026. Updated criteria for Besremi (ropeginterferon alfa-2b-njft) adding the quantity is limited to 2 pens or syringes every 28 days. Updated criteria for Daybue (trofinetide) and Daybue Stix (trofinetide) adding a quantity limit per 30 days. Updated Imcivree (setmelanotide) adding criteria for the treatment of acquired hypothalamic obesity, and added a quantity limit per 30 days. Updated criteria for Zycubo (copper histidinate) to add a specialist requirement, revise diagnostic criteria by removing serum copper and ceruloplasmin level requirements, include plasma catecholamine analysis as one of the acceptable diagnostic options,

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	and updated initial authorization length of approval to 12 months. Updated criteria for Voxzogo (vosoritide) adding medication will not be used concurrently with Yuviwel (navepegritide). Added Yuviwel (navepegritide) to the policy to increase linear growth in individuals with achondroplasia. Updated Bylvay, Crenessity, Ctexli, Daybue, Daybue Stix, dichlorphenamide, Enjaymo, Firdapse, Forzinity, Gamifant, Givlaari, Keveyis, Livmarli, Nulibry, Ormalvi, Oxlumo, Pyrukynd, Rivfloza, Ryplazim, Sylvant, Vykat XR initial approval authorization length from 6 months to 12 months. Removed reference to non-formulary exception reviews.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2026 Premera All Rights Reserved.

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