Pharmacy Management Drug Policy

SUBJECT: Inborn Errors of Metabolism (IEM)
POLICY NUMBER: PHARMACY-23
EFFECTIVE DATE: 03/01/2007
LAST REVIEW DATE: 07/08/2025

If the member's subscriber contract excludes coverage for a specific service or prescription drug, it is not covered under that contract. In such cases, medical or drug policy criteria are not applied. This drug policy applies to the following line/s of business:

Policy Application

Category:	☒ Commercial Group (e.g., EPO, HMO, POS, PPO)	☒ Medicare Advantage
	☒ On Exchange Qualified Health Plans (QHP)	☐ Medicare Part D
	☒ Off Exchange Direct Pay	☒ Essential Plan (EP)
	☒ Medicaid & Health and Recovery Plans (MMC/HARP)	☒ Child Health Plus (CHP)
	☐ Federal Employee Program (FEP)	☐ Ancillary Services
	☒ Dual Eligible Special Needs Plan (D-SNP)	

DESCRIPTION:

Inborn errors of metabolism (IEMs) comprise a wide array of genetic diseases including disorders of protein, carbohydrate, and fat metabolism, lysosomal storage disorders, fatty acid oxidation defects, and mitochondrial and peroxisomal disorders. Although errors of metabolism are more common in infancy and childhood, presentation can occur at any time, even in adulthood. In many of the disorders, problems arise secondary to the accumulation of substances which are toxic or interfere with normal functions of the body. Or patients are unable to synthesize essential compounds necessary for adequate growth and maintenance of health. Enzyme replacement has become a beneficial treatment strategy for many of these previously untreatable disorders. IEMs are often treated with FDA approved replacement enzymes that may be designated as orphan drugs or investigational agents. Prompt institution of therapy is important because delay in the recognition and treatment of IEMs may result in long-term neurologic impairment or even death.
Drug therapies to treat various rare diseases due to genetic mutations are also included within this policy.

This policy is applicable to drugs that are included on a specific drug formulary. If a drug referenced in this policy is non-formulary, please reference the Coverage Exception Evaluation Policy for All Lines of Business Formularies Policy for review guidelines.

Approval time periods: Unless otherwise noted within individual drug criteria, approval time periods are defined under Policy Guidelines at the end of this policy

DRUG SPECIFIC POLICIES/CRITERIA:

Amvuttra (vutrisiran)-Medical
A. Polyneuropathy of Hereditary Transthyretin-mediated Amyloidosis (hATTR) 1. Member is 18 years of age or older **AND** 2. Prescribed by specialist experienced in the diagnosis of hATTR amyloidosis such as hematologist-oncologist, neurologist, gastroenterologist, geneticist, or nephrologist **AND** 3. Diagnosis of hATTR amyloidosis with polyneuropathy **AND** 4. Documentation of a pathologic mutation in the transthyretin (TTR) gene (via genetic testing / DNA sequencing) **AND** 5. A baseline Polyneuropathy disability (PND) score of IIIb or lower **AND** 6. Must also have symptoms consistent with polyneuropathy attributed to hATTR and other causes of neuropathy have been excluded: a. Peripheral sensorimotor polyneuropathy symptoms, such as: tingling or increased pain in the hands/feet/arms, loss of feeling in the hands/feet, numbness or tingling in the wrists, carpal tunnel syndrome, loss of ability to sense temperature or pain, difficulty with fine motor skills, weakness/numbness/pain in the legs, difficulty walking, seizures, headaches, inability to perform activities of daily living (ADLs) b. Autonomic neuropathy symptoms such as: orthostasis, abnormal sweating, sexual dysfunction, recurrent urinary tract infection, dysautonomic symptoms of constipation, diarrhea, nausea, vomiting, anorexia, and early satiety **AND** 7. Patient has not been the recipient of an orthotopic liver transplant (OLT) **AND** 8. Must be administered by a healthcare professional **AND** 9. Amvuttra must be used as monotherapy and will NOT be covered in combination with Tegsedi (inotersen), Onpattro (patisiran), Wainua (eplontersen) or any other polyneuropathy of hereditary transthyretin mediated amyloidosis (hATTR) disease specific therapy. Please note: Prior approval for any other polyneuropathy of hereditary transthyretin mediated amyloidosis (hATTR) specific treatment will be terminated upon approval of Amvuttra a. Amvuttra will not be approved for use in combination with tafamidis (Vyndamax/Vyndaqel) or acoramidis (Attruby) **AND** 10. Initial approval for Amvuttra will be for one year. 11. Continued approval beyond on year and recertification every two years will require: 12. Documentation of improvement **OR** stability of disease and symptoms with Amvuttra (via lab reports, progress notes, neurologic exam, PND) **B. Cardiomyopathy of Wild-type or Hereditary Transthyretin-mediated Amyloidosis (ATTR-CM)** 1. The patient must be 18 years of age or older **AND** 2. The medication must be prescribed by or in consultation with a physician who specializes in the treatment of amyloidosis, such as a cardiologist **AND** 3. The patient must have a diagnosis of cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) **AND** 4. The diagnosis must be confirmed by one the following: a. 99mTechnetium-labeled pyrophosphate cardiac imaging (nuclear scintigraphy) positive for transthyretin (TTR) amyloid **OR** b. Amyloid deposits identified on cardiac biopsy AND presence of a variant TTR genotype and/or TTR precursor protein identification by molecular genetic testing (i.e., immunohistochemistry, scintigraphy, or mass spectrometry) or next-generation sequencing (NGS) **AND** 5. The patient must have a clinical history of heart failure classified as New York Heart Association Class I – III, with at least one prior hospitalization for heart failure **OR** in the absence of prior hospitalization must have clinical evidence of heart failure with signs/symptoms (such as shortness

of breath, peripheral edema, ascites, elevated jugular pressure, etc.) requiring treatment with a diuretic for improvement **AND**

6. The patient must have evidence of cardiac involvement seen on echocardiography and/ or cardiac magnetic imaging, such as thickened left ventricle wall / septum **AND**
7. The patient must have had a trial of tafamidis (Vyndamax/Vyndaqel) or acoramidis (Attruby) for at least 6 months, unless contraindicated or not clinically appropriate.
    a. The trial must provide evidence that treatment with tafamidis (Vyndamax/Vyndaqel) or acoramidis (Attruby) is no longer sufficient to control disease progression as demonstrated by at least one of the following (i, ii, iii, **OR** iv):
        i. Sustained elevation of cardiac biomarkers (e.g., NT-proNBP or Troponin)
        ii. Worsening of cardiac function (e.g., decline in left ventricular ejection fraction or increased left ventricular wall thickness on imaging)
        iii. Clinical deterioration indicated by a decrease in 6-Minute Walk Test performance
        iv. Increasing amyloid burden on bone scintigraphy or cardiac MRI
8. To effectively monitor treatment process and clinical improvement, documentation of the following clinical parameters is required prior to initiating therapy:
    a. Cardiac Biomarkers (NT-proBNP or troponin)
    b. TTR Protein Level (i.e., serum TTR)
    c. 6-Minute Walk Test
9. Recertification requirements
    a. First recertification (after initial approval) will require documentation of the following:
        i. A reduction in cardiac stress or damage, or improving function as evidenced by a decrease in NT-proBNP or troponin from baseline
        ii. A reduction in TTR production as evidenced by a decrease in serum TTR from baseline
        iii. Improvement or stabilization of the 6-Minute Walk test compared to baseline values
    b. Subsequent recertifications (after first recertification) will require documentation of the following:
        i. Continued reduction or stabilization of NT-proBNP or troponin (no increase in biomarker)
        ii. Continued suppression of TTR production (no increase in serum TTR)
        iii. Continued improvement or stabilization of the 6-Minute Walk test compared to baseline values
10. Amvuttra must be used as monotherapy
    a. Amvuttra will not be covered for use in combination with tafamidis (Vyndamax/Vyndaqel) or acoramidis (Attruby) for the treatment of ATTR-CM
        i. The concurrent use of transthyretin (TTR) stabilizers (e.g., tafamidis [Vyndamax/Vyndaqel] or acoramidis [Attruby]) and TTR silencers (e.g., vutrisiran [Amvuttra])) is considered not medically necessary due to the absence of clinical evidence demonstrating additional therapeutic benefit (e.g., additional reduction in mortality or hospitalization) and safety.
11. Amvutrra will NOT be covered in the following scenarios as there are no data supporting the safety and efficacy at this time:
    a. New York Heart Association Class IV heart failure
    b. Presence of primary (light chain) amyloidosis, secondary (AA) amyloidosis or any other non-ATTR amyloidosis
    c. Use in combination with Onpattro (patisiran), Tegsedi (inotersen), or Wainua (eplontersen)
12. Approved Dosage: See Prescribing Information
13. Approval will be for 1 year at a time
14. Quantity Limit: 1 syringe per 84 days

Aqneursa (levacetylleucine)-Rx
1. Must be prescribed by or in consultation with a geneticist, neurologist, metabolic disorder specialist, or a physician who specializes in the treatment of Niemann-Pick disease type C (NPC) **AND** 2. Must have a diagnosis of NPC confirmed with documentation of biallelic pathogenic variants in either NPC1 or NPC2 identified by molecular genetic testing **AND** 3. Must weigh 15 kg or greater **AND** 4. Must have documentation of neurological manifestations of the disease (e.g., dysphagia, cognitive and/or speech impairment, progressive ataxia, dystonia, dysarthria, vertical supranuclear gaze palsy) **AND** 5. Must provide documentation of functional Scale for the Assessment and Rating of Ataxia (fSARA) score at baseline (prior to initiating Aqneursa) which will be used to assess clinical response (see Appendix for scale). 6. Aqneursa will not be authorized for any non-FDA approved indication **AND** 7. Aqneursa will not be authorized for use in combination with Miplyffa (arimoclomol) as this combination has not been studied **AND** 8. Initial approval and recertification will be for 12 months at a time. Continued approval will require the patient has demonstrated stabilization or improvement in the fSARA score compared to baseline. 9. Quantity limit: 112 packets/28 days
Attruby (acoramidis)- Rx
1. The patient must be 18 years of age or older **AND** 2. The medication must be prescribed by or in consultation with a physician who specializes in the treatment of amyloidosis, such as a cardiologist **AND** 3. The patient must have a diagnosis of cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) **AND** 4. The diagnosis must be confirmed by one the following: a. 99mTechnetium-labeled pyrophosphate cardiac imaging (nuclear scintigraphy) positive for TTR amyloid **OR** b. Amyloid deposits identified on cardiac biopsy **AND** presence of a variant TTR genotype and/or TTR precursor protein identification by molecular genetic testing (i.e., immunohistochemistry, scintigraphy, or mass spectrometry) or next-generation sequencing (NGS) **AND** 5. The patient must have a clinical history of heart failure classified as New York Heart Association Class I – III, with at least one prior hospitalization for heart failure **OR** in the absence of prior hospitalization must have clinical evidence of heart failure with signs/symptoms (such as shortness of breath, peripheral edema, ascites, elevated jugular pressure, etc.) requiring treatment with a diuretic for improvement **AND** 6. The patient must have evidence of cardiac involvement seen on echocardiography and/ or cardiac magnetic imaging, such as thickened left ventricle wall / septum **AND** 7. To effectively monitor treatment process and clinical improvement, documentation of the following clinical parameters is required prior to initiating therapy: a. Cardiac Biomarkers (NT-proBNP or troponin) b. TTR Protein Level (i.e., serum TTR) c. 6-Minute Walk Test 8. Recertification requirements a. First recertification (after initial approval) will require documentation of the following: i. A reduction in cardiac stress or damage, or improving function as evidenced by a decrease in NT-proBNP or troponin from baseline ii. Improvement or stabilization of the 6-Minute Walk test compared to baseline values b. Subsequent recertifications (after first recertification) will require documentation of the following: i. Continued reduction or stabilization of NT-proBNP or troponin (no increase in biomarker)

ii. Continued improvement or stabilization of the 6-Minute Walk test compared to baseline values

9. Attruby must be used as monotherapy
    a. Attruby will not be covered for use in combination with tafamidis (Vyndamax/Vyndaqel) or vutrisiran (Amvuttra) for the treatment of ATTR-CM
        i. The concurrent use of transthyretin (TTR) stabilizers (e.g., tafamidis [Vyndamax/Vyndaqel] or acoramidis [Attruby]) and TTR silencers (e.g., vutrisiran [Amvuttra])) is considered not medically necessary due to the absence of clinical evidence demonstrating additional therapeutic benefit (e.g., additional reduction in mortality or hospitalization) and safety.
10. Attruby will NOT be covered in the following scenarios as there are no data supporting their safety and efficacy at this time:
    a. New York Heart Association Class IV heart failure
    b. Presence of primary (light chain) amyloidosis, secondary (AA) amyloidosis or any other non-ATTR amyloidosis
    c. Use in combination with Onpattro (patisiran), Tegsedi (inotersen), or Wainua (eplontersen)
11. Approved Dosage: See Prescribing Information
12. Quantity limit: 120 tablets/30 days
13. Approval will be for 1 year at a time

Brineura (cerliponase alfa)-Medical

1. Must prescribed by or in consultation with a provider that specializes in the treatment of neuromuscular disorders and/or late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency and is knowledgeable in intraventricular administration **AND**
2. Must have a diagnosis of late infantile CLN2 disease confirmed by deficient TPP1 enzyme activity (in leukocytes, fibroblasts, or dried blood spots); or detection of two pathogenic mutations *in trans* in the TPP1/CLN2 gene **AND**
3. Must have a score of <6 on CLN2 clinical rating scale for motor and language function (see below for CLN2 rating scale), **AND**
4. Brineura is contraindicated in patients with ventriculoperitoneal shunts (used to drain extra fluid around the brain) and those with acute intraventricular access device-related complications (e.g., leakage, device failure, device-related infection).
5. Initial approval will be for 6 months and requires a motor domain of the CLN2 Clinical Rating Scale score ≥ 1
6. Continued approval beyond 6 months (see Approval Time Periods section for recertification time based on site of care) requires documentation of positive response to therapy defined as no decline or decline of one category decline and a score > 0.
    - Decline was defined as having an unreversed (sustained) 2 category decline or an unreversed score of 0 in the motor domain of the CLN2 Clinical Rating Scale

Additional Drug Information:
The motor domain of the CLN2 Clinical Rating Scale is scored as follows:

Score	Motor Function:
3	Walks normally
2	Intermittent falls, clumsiness, obvious instability
1	No unaided walking OR crawling only
0	Immobile, mostly bedridden

Carbaglu and generic carglumic acid– Rx

1. Patient must be followed by a physician experienced in metabolic disorders, **AND**
2. Patient must have a diagnosis of acute or chronic hyperammonemia due to the deficiency of the hepatic enzyme, N-acetylglutamate synthase (NAGs) confirmed via genetic testing or enzyme analysis alone or in combination with laboratory tests specific for this diagnosis including measurement of ammonia, plasma citrulline, plasma arginine, orotic acid
3. For acute hyperammonemia due to the deficiency of the hepatic enzyme, N-acetylglutamate synthase (NAGs), the patient must be receiving concomitant ammonia lowering therapies such as alternate pathway medications, hemodialysis, and dietary protein restriction **OR**
4. Patient must have a diagnosis of acute hyperammonemia due to propionic acidemia or methylmalonic acidemia, the patient must be receiving standard therapies including a combination of protein restriction, intravenous (IV) glucose, insulin and/or L-carnitine.
5. Current body weight and requested dose regimen must be submitted for initial review and each recertification request
6. All requests for brand Carbaglu (initial and recertification) will require documentation of severe intolerance to generic carglumic acid.
7. Initial approval will be for one year
8. Recertification every 2 years will require documentation of normalization of plasma ammonia levels, improvement in any clinical symptoms and stability on the requested therapy

Recommended Dosing:

1. Dosage for **acute** hyperammonemia is 100-250mg/kg/day. Dose should be divided to 2-4 times per day and rounded to the nearest 100mg (1/2 TABLET)
2. Dosage for **maintenance** should be targeted for normal plasma ammonia level for age (usually less than 100mg/kg/day)
3. Dosage in patients with **acute** hyperammonemia due to propionic acidemia or methylmalonic acidemia is 150 mg/kg/day for patients ≤ 15 kg and 3.3 g/m2/day for patients > 15 kg. Divide the daily dosage into two equal doses, round up to the next multiple of 50 mg (i.e., one-quarter of a Carbaglu tablet), and administer doses 12 hours apart.

Cerdelga (eliglustat) – Rx

1. Prescribed by or in consultation with a physician knowledgeable in the management of Gaucher disease, **AND**
2. Must have a confirmed diagnosis of Type 1 Gaucher disease (see Diagnosis section below for requirements), **AND**
   a**. Adults: Type 1 (nonneuronopathic)** Gaucher disease confirmed by:
   - Biochemical assay of glucocerebrosidase activity in white blood cells (WBCs) or skin fibroblasts less than or equal to 30% **OR**
   - Genotype mutation of two mutant alleles of the glucocerebrosidase gene **AND**
   - Symptomatic manifestations of the disease
     - Skeletal disease as demonstrated by radiological evidence of joint deterioration, pathological fracture, osteopenia, avascular necrosis, osteosclerosis, marrow infiltration, lytic lesions, or Erlenmeyer flask deformity) **OR**
     - Hemoglobin ≤11.5 for females and ≤12.5 g/dl for males (or 1.0 g/dL below the lower limit of normal for age and sex), platelet count <= 60,000 mm^3, spleen > 15 times normal size, liver > 2.5 times normal size.

   b**. Children Type 1 (nonneuronopathic):** less than 18 years of age with Type 1 Gaucher disease confirmed by:
   - Biochemical assay of glucocerebrosidase activity in WBC's or skin fibroblasts is less than or equal to 30%. **OR**

- Genotype mutation of two mutant alleles of the glucocerebrosidase gene **AND**
- Symptomatic manifestations of the disease
  - Abdominal or bone pain, delayed growth, impaired psychomotor development, fatigue, exertional limitations, marrow infiltration, organomegaly, weakness and cachexia.

3. Must be ≥ 18 years of age, **AND**
4. Not covered in patients with pre-existing cardiac disease, long QT syndrome, and concomitant use of Class IA and Class III antiarrhythmics, **AND**
5. Cerdelga will not be approved in combination with enzyme replacement therapy (taliglucerase alfa, imiglucerase, or velaglucerase alfa) as this is considered investigational, **AND**
6. Must be designated as a CYP2D6 extensive metabolizer (EM), intermediate metabolizer (IM), or poor metabolizer (PM) as detected by an FDA-cleared test to determine appropriate dosing, **AND**
7. Dosing guidelines:
   a. CYP2D6 EMs or IMs: approved dose is 84 mg orally **twice daily**
   b. CYP2D6 PMs: approved dose is 84 mg orally **once daily**
   c. CYP2D6 ultra-rapid metabolizers (URM) and CYP2D6 indeterminate metabolizers are excluded from coverage.
      - CYP2D6 URMs may not achieve adequate concentrations of CERDELGA to achieve a therapeutic effect
      - A specific dosage cannot be recommended for those patients whose CYP2D6 indeterminate
   d. The following drug interactions result in contraindication to Cerdelga and will not be covered:
      - CYP2D6 EMs or IMs taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor.
      - CYP2D6 IMs or PMs taking a strong CYP3A inhibitor.
   e. Specific dosing information is listed in the Cerdelga package insert.
8. After the initial one-year approval, recertification every 2 years requires the patient not be on strong or moderate CYP2D6/3A inhibitors which results in contraindications to Cerdelga, documentation of improvement in any clinical symptoms and stability on the requested therapy.

Cerezyme (imiglucerase) – Medical

1. Prescribed by or in consultation with a physician knowledgeable in the management of Gaucher disease, **AND**
2. Must have a confirmed diagnosis of Gaucher disease (see Diagnosis section below for requirements), **AND**
   a. **Adults: Type 1 (nonneuronopathic)** Gaucher disease confirmed by:
      - Biochemical assay of glucocerebrosidase activity in white blood cells (WBCs) or skin fibroblasts less than or equal to 30% **OR**
      - Genotype mutation of two mutant alleles of the glucocerebrosidase gene **AND**
      - Symptomatic manifestations of the disease
        - Skeletal disease as demonstrated by radiological evidence of joint deterioration, pathological fracture, osteopenia, avascular necrosis, osteosclerosis, marrow infiltration, lytic lesions, or Erlenmeyer flask deformity) **OR**
        - Hemoglobin ≤11.5 for females and ≤12.5 g/dl for males (or 1.0 g/dL below the lower limit of normal for age and sex), platelet count <= 60,000 mm^3, spleen > 15 times normal size, liver > 2.5 times normal size.
   b. **Children Type 1 (nonneuronopathic):** less than 18 years of age with Type 1 Gaucher disease confirmed by:
      - Biochemical assay of glucocerebrosidase activity in WBC's or skin fibroblasts is less than or equal to 30%. **OR**
      - Genotype mutation of two mutant alleles of the glucocerebrosidase gene **AND**
      - Symptomatic manifestations of the disease

- Abdominal or bone pain, delayed growth, impaired psychomotor development, fatigue, exertional limitations, marrow infiltration, organomegaly, weakness and cachexia.

c. **Adults and Children Type III (neuronopathic):** Enzyme replacement therapy is considered off-label for this diagnosis; however, consideration will be given for the following scenarios in which ERT has been shown to be beneficial for hematological and visceral disease
- Individuals with chronic (not acute) neuronopathic Gaucher disease type 3
- Siblings of individuals with chronic neuronopathic Gaucher disease who have proven diagnosis
- Individuals with high-risk genotypes: L444P/L444P (c.1448T>C homozygote), D409H/D409H (c.1342G>C homozygote), L444P/D409H (c.1448T>C/c.1342G>C heterozygote)
- Onset of severe systemic disease at age ≤ 2 years of age

3. Must be ≥ 2 years of age, **AND**
4. Cerezyme is administered by intravenous infusion by a healthcare professional and is covered under the medical benefit, **AND**
5. All requests for Cerezyme will be required to use Elelyso (taliglucerase alfa) except in the following situation:
   a. Cerezyme (imiglucerase) will be approved for children between age 2 and less than 4 years of age. Requests for Cerezyme as continued therapy for children at 4 years of age or older will be required to use Elelyso or document serious side effects or drug failure to Elelyso, **AND**
6. Cerezyme will not be approved in combination with any other enzyme replacement therapy for Gaucher disease

Current body weight and requested dose regimen must be submitted for initial review and each recertification request

Cholbam (cholic acid)- Rx

1. Must have a diagnosis of bile acid synthesis disorder due to single enzyme defect (SED) **OR**
2. Must be used as an adjunctive treatment of peroxisomal disorder (PD) including Zellweger spectrum disorders, in patients who show signs and symptoms of liver disease, steatorrhea (fatty stools), or complications from decreased fat-soluble vitamins absorption (A, D, E, K) **AND**
3. Diagnosis must be confirmed via gas chromatography-mass spectrometry analysis of the urine, which positively identifies elevated bile acids **AND**
4. Must have elevated serum aminotransferases with normal serum gamma glutamyl transferase, **AND**
5. Member must be seen by a hepatologist, or gastroenterologist **AND**
6. Must be at least 3 weeks old, **AND**
7. Current body weight and requested dose regimen must be submitted for initial review and each recertification request.
8. Initial approval will be for 3 months. Discontinue Cholbam if liver function does not improve within 3 months of starting treatment, if complete biliary obstruction develops, or if there are persistent clinical or laboratory indicators of worsening liver function or cholestasis; continue to monitor liver function and consider restarting a lower dose when parameters return to baseline.
9. Continued approval beyond 3 months and recertification every 2 years will require documentation of improved liver function via aminotransferase lowering as well as improvement in any clinical symptoms and stability on the requested therapy.

<u>Recommended Dosing:</u>

- Recommended initial dosage is 10 to 15 mg/kg/day (given in 1 or 2 divided doses) using available 50 mg and 250 mg capsules and rounded to the nearest whole capsule strength.
- For patients with concomitant familial hypertriglyceridemia, the recommended dosage is 11 to 17 mg/kg (given in 1 or 2 divided doses).

Crysvita (burosumab-twza) - Medical
Crysvita, a fibroblast growth factor 23 (FGF23) blocking antibody, blocks the activity of FGF23, thereby increasing serum phosphorus and active vitamin D and is considered medically necessary if all the Universal criteria **AND** disease specific criteria have been met: 1. Universal criteria for all diagnoses: a. Must be prescribed by an Endocrinologist, Nephrologist or another specialist experienced in the treatment of metabolic bone disorders, **AND** b. Patient has serum phosphorus level below normal for age and gender (refer to lab report for reference ranges or refer to the table below). i. Recent lab report with reference ranges is required. ii. Administration of Crysvita when serum phosphorus is within or above the normal range for age is contraindicated, **AND** c. Patient has a baseline tubular reabsorption of phosphate corrected for glomerular filtration rate (TmP/GFR) below the normal range for age and gender, **AND** d. Patient does not have severe renal impairment (eGFR < 30mL/min/1.73m^3) or end stage renal disease (ESRD) as this is contraindicated, **AND** e. Oral phosphate and/or active Vitamin D analogs have been discontinued at least one week prior to the start of Crysvita, as use in combination with Crysvita is contraindicated, **AND** f. Crysvita must be administered as a subcutaneous (SC) injection by a healthcare provider, **AND** 2. X-Linked Hypophosphatemia (XLH) must also meet the following requirements *in addition to the Universal criteria* above: a. Must be 6 months of age or older, **AND** b. Diagnosis of X-Linked Hypophosphatemia has been confirmed by at least one of the following i. Elevated Serum fibroblast growth factor 23 (FGF23) level > 30 pg/mL **OR** ii. Molecular genetic testing confirming PHEX-gene (phosphate regulating gene with homology to endopeptidases located on the X chromosome) mutation, **AND** c. One of the following: i. Patient's epiphyseal plate has not fused (i.e., children) **OR** ii. Patient's epiphyseal plate has fused (i.e., adult / adolescent) - coverage is limited to symptomatic patients with documentation of clinical signs/symptoms such as: stress fractures of lower extremities, pseudofractures, bone pain, short stature, bowed legs, waddling gait, dental abnormalities (abscesses or tooth loss), evidence of enthesopathy (calcification of tendons, ligaments, and joint capsules), **AND** d. Initial approval is for one year, e. Recertification and every 2 years thereafter will require submission of both of the following: • Lab report(s) with reference range documenting increased serum phosphorus level from baseline. Serum phosphorus must NOT be above the upper limit of the laboratory normal reference range. Serum phosphorus levels exceeding 5mg/dL (pediatrics) or above the upper limit of normal (adults) require dose interruption per US Food and Drug Administration approved labeling and request must include physician treatment plan. • Documentation of a positive response to therapy: improvement in symptoms (such as: reduction of bone pain, enhanced mobility, fracture reduction/healing, improvement of skeletal deformities, linear growth), improvement in radiographic imaging, normalization of laboratory findings such as increase serum phosphorus, reduction in serum total alkaline phosphatase activity. f. Dosing for XLH is as follows: i. Pediatric patients aged 6 months and older: • Weight less than 10 kg: starting dose regimen is 1 mg/kg of body weight rounded to the nearest 1 mg, administered every two weeks.

- Weight more than 10 kg: starting dose regimen is 0.8 mg/kg of body weight rounded to the nearest 10 mg, administered every two weeks.
- Dose may be increased up to approximately 2 mg/kg (maximum 90 mg), administered every two weeks to achieve normal serum phosphorus.
- The minimum starting dose is 10 mg up to a maximum dose of 90 mg.
- Dosage is adjusted no more frequently than every 4 weeks based on serum phosphorus levels.

ii. Adult patients 18 years of age and older
- Starting dose is 1mg/kg body weight, rounded to the nearest 10mg administered every 4 weeks.
- Dosage is adjusted no more frequently than every 4 weeks based on serum phosphorus levels.
- Maximum dose is 90mg every 4 weeks.

iii. Current body weight and requested dose regimen must be submitted for initial review and each recertification request

iv. Doses above 90mg will not be permitted for children or adults

3. Tumor-Induced Osteomalacia must meet the following requirements *in addition to Universal Criteria above*:
   a. Must be 2 years of age or older, **AND**
   b. Must have a diagnosis of tumor-induced osteomalacia associated with phosphaturic mesenchymal tumor with documentation that the tumor cannot be curatively resected or localized (cannot determine location of tumor), **AND**
   c. Documentation of an elevated FGF23 level (e.g., FGF23 > 100pg/mL), **AND**
   d. Must have symptoms consistent with fibroblast growth factor 23 (FGF23)-related hypophosphatemia/osteomalacia such as muscle weakness, bone pain, fractures and weakening of the bones, **AND**
   e. Dosing for TIO is as follows:
      i. Pediatric patients aged 2 years and older:
         - Starting dose is 0.4mg/kg of body weight rounded up to the nearest 10mg every 2 weeks.
         - Dose may be increased up to 2mg/kg not to exceed 180mg, administered every 2 weeks

      ii. Adult patients 18 years of age and older:
         - Starting dose is 0.5mg/kg every four weeks
         - Dose may be increased up to 2mg/kg not to exceed 180mg, administered every 2 weeks.

      iii. Current body weight and requested dose regimen must be submitted for initial review and each recertification request.

      iv. Doses above 180mg will not be permitted for children or adults
   f. Initial approval is for 6 months, **AND**
   g. Recertification once yearly thereafter will require submission of both of the following:
      - Lab report(s) with reference range documenting increased serum phosphorus level from baseline. Serum phosphorus must NOT be above the upper limit of the laboratory normal reference range. Serum phosphorus levels exceeding the upper limit of normal require dose interruption per US Food and Drug Administration approved labeling and request must include physician treatment plan.
      - Documentation of a positive response to therapy including improvement in any clinical symptoms (for example: a reduction of bone pain, enhanced mobility, fracture reduction/healing, improvement of skeletal deformities) and
      - IF a patient undergoes treatment of the underlying tumor (i.e., surgical excision or radiation therapy) Crysvita treatment should be interrupted, and serum phosphorus reassessed after

treatment has been completed. Crysvita dose should be restarted at the patient's initiation dose if serum phosphorus remains below the lower limit of normal.

Crysvita is available in a 10 mg/mL, 20 mg/mL, and 30 mg/mL single dose vial.

Doses of 10mg, 20mg, and 30mg should use the available strength product. Higher doses should use a combination of vials equal to the required dose avoiding medication waste. For example: 50mg dose = one 20mg/ml vial + one 30mg/ml vial (not 2 x 30mg vials). Requests will be reviewed for dose efficiency.

Fasting serum phosphorus (Phosphate, PO_4) reference ranges for age (Use only if reference range is not included on lab report):	
Reference range for FEMALES	Reference range for MALES
1-7 years: 4.3-5.4 mg/dL 8-13 years: 4.0-5.2 mg/dL 14-15 years: 3.5-4.9 mg/dL 16-17 years: 3.1-4.7 mg/dL > or =18 years: 2.5-4.5 mg/dL Reference values have not been established for patients that are less than 12 months of age.	1-4 years: 4.3-5.4 mg/dL 5-13 years: 3.7-5.4 mg/dL 14-15 years: 3.5-5.3 mg/dL 16-17 years: 3.1-4.7 mg/dL > or =18 years: 2.5-4.5 mg/dL Reference values have not been established for patients that are less than 12 months of age.

Ctexli (chenodiol)-Rx

1. Must be 18 years of age or older **AND**
2. Must be prescribed by, or in consultation with, a hepatologist, metabolic specialist, or gastroenterologist **AND**
3. Must have a diagnosis of cerebrotendinous xanthomatosis (CTX) with genetic testing confirming biallelic pathogenic variants in the CYP27A1 gene **AND**
4. Must have documentation of at least **ONE** of the following parameters (baseline value must be provided and will be used to assess response to therapy):
   a. Elevated blood cholestanol **OR**
   b. Elevated blood or urine bile alcohol (e.g., 23S-pentol)
5. Ctexli will not be authorized for treatment of gallstones
6. Ctexli will not be authorized for use in combination with Cholbam, cholestyramine, or colestipol.
7. Initial approval will be for 6 months. Recertification will be for 12 months at a time and require documentation of improvement from baseline (upon initial recertification) and/or maintenance of improvement of either:
   a. Blood cholestanol **OR**
   b. Blood or urine bile alcohol (e.g., 23S-pentol)
8. Quantity limit: 90 tablets per 30 days

Dojolvi (tripheptanoin oral liquid) - Rx

1. Must be prescribed by, or in consultation with, a metabolic disease specialist knowledgeable in the management of long-chain fatty acid oxidation disorders and their dietary management, **AND**
2. Must have a molecularly confirmed long-chain fatty acid oxidation disorder based on at least two of the following (i, ii and/or iii). Of note, infants with positive newborn screening on dried blood spot analysis are required to have confirmatory testing
   i. Molecular genetic testing identifying biallelic pathogenic variants confirming a long-chain fatty acid oxidation disorder (such as in CPT1A, CPT2, ACADVL, HADHA or HADHB), **AND/OR**
   ii. Abnormal acylcarnitine analysis on biochemical testing of plasma, **AND/OR**
   iii. Biochemical analysis confirming diminished enzyme activity (such as in cultured skin fibroblasts, muscle, liver, leukocytes), **AND**
3. Must have evidence of clinical signs and/or symptoms associated with LC-FAOD such as hypoglycemia, hepatopathy, cardiomyopathy, skeletal myopathy, rhabdomyolysis, exercise intolerance, for example, despite current management such as a low-fat, high-carbohydrate diet;

avoidance of fasting and/or the use of a medium-chain triglyceride (MCT) oil, or as noted below in i **AND/OR** ii:
   i. Patients who are infants or early childhood (3-5 years old) at the time of the request who were diagnosed via a Newborn Screening program with confirmatory testing will not be required to be symptomatic
   ii. Plan will consider coverage for asymptomatic children who have a confirmed diagnosis with a positive family history of severe disease, or positive genotype indicating severe form of the disease, **AND**
4. Provider must attest/confirm that medium-chain triglyceride (MCT) oil products will be discontinued prior to the start of Dojolvi, **AND**
5. Documentation of the patient's total prescribed Daily Caloric Intake (DCI) and Target percentage of daily caloric intake prescribed and Target Total Daily Dosage (mL) to be administered must be provided with each review.
6. Quantity limit of 500ml per 30 days. Requests for quantities above this limit will be evaluated based on the dosing documentation provided.
7. Initial approval will be for 6 months
8. Recertification after 6 months and yearly thereafter will require the following:
   a. Dojolvi continues to be used as monotherapy [i.e.: not in combination with any other medium chain triglyceride (MCT) products].

Recommended dosing:
   a. Target daily dose of Dojolvi is up to 35% of the patient's total prescribed daily caloric intake (DCI) divided into at least four doses and administered orally diluted with semi-solid foods, liquids, or formula or enterally via a silicone or polyurethane feeding tube.
   b. The total daily dosage is determined using the following calculation:
      • Caloric value of DOJOLVI = 8.3 kcal/mL
      • Round the total daily dosage to the nearest whole number.

$$\text{Total daily dose (\_\_\_ ml)} = \frac{\text{Patients DCI (\_\_\_kcal) x Target \_\_\_\_\% dose of DCI}}{\text{8.3 kcal/mL of Dojolvi}}$$

Elaprase (idursulfase)-Medical

1. Patient must be followed by a physician experienced in metabolic disorders, **AND**
2. Must have a diagnosis of Hunter Syndrome (mucopolysaccharidosis II) confirmed by biochemical enzyme analysis for iduronate sulfatase deficiency in white blood cells or cultured skin fibroblasts **AND**
3. Must have an affected 1st degree relative **OR** clinical symptoms of the disease such as: progressive coarsening of facial features, short stature, joint stiffness, hepatosplenomegaly, hernias, ivory colored papular skin lesions located on the upper back and/or lateral upper arms and thighs, mental retardation, deafness, cerebral ventricular dilation, mild dysostosis multiplex of bone, hypertrichosis, thickened skin, or Mongolian spots. **AND**
4. Must be ≥16 months of age
5. Current body weight and requested dose regimen must be submitted for initial review and each recertification request.

Recommended dosing: 0.5mg/kg IV infusion once a week

Elelyso (taliglucerase alfa) – Medical

1. Prescribed by or in consultation with a physician knowledgeable in the management of Gaucher disease, **AND**
2. Must have a confirmed diagnosis of Gaucher disease (see Diagnosis section below for requirements), **AND**

a. **Adults: Type 1 (nonneuronopathic)** Gaucher disease confirmed by:
   - Biochemical assay of glucocerebrosidase activity in white blood cells (WBCs) or skin fibroblasts less than or equal to 30% **OR**
   - Genotype mutation of two mutant alleles of the glucocerebrosidase gene **AND**
   - Symptomatic manifestations of the disease
     - Skeletal disease as demonstrated by radiological evidence of joint deterioration, pathological fracture, osteopenia, avascular necrosis, osteosclerosis, marrow infiltration, lytic lesions, or Erlenmeyer flask deformity) **OR**
     - Hemoglobin ≤11.5 for females and ≤12.5 g/dl for males (or 1.0 g/dL below the lower limit of normal for age and sex), platelet count <= 60,000 mm^3, spleen > 15 times normal size, liver > 2.5 times normal size.

b. **Children Type 1 (nonneuronopathic):** less than 18 years of age with Type 1 Gaucher disease confirmed by:
   - Biochemical assay of glucocerebrosidase activity in WBC's or skin fibroblasts is less than or equal to 30%. **OR**
   - Genotype mutation of two mutant alleles of the glucocerebrosidase gene **AND**
   - Symptomatic manifestations of the disease
     - Abdominal or bone pain, delayed growth, impaired psychomotor development, fatigue, exertional limitations, marrow infiltration, organomegaly, weakness and cachexia.

a. **Adults and Children Type III (neuronopathic):** Enzyme replacement therapy is considered off-label for this diagnosis; however, consideration will be given for the following scenarios in which ERT has been shown to be beneficial for hematological and visceral disease
   - Individuals with chronic (not acute) neuronopathic Gaucher disease type 3
   - Siblings of individuals with chronic neuronopathic Gaucher disease who have proven diagnosis
   - Individuals with high-risk genotypes: L444P/L444P (c.1448T>C homozygote), D409H/D409H (c.1342G>C homozygote), L444P/D409H (c.1448T>C/c.1342G>C heterozygote)
   - Onset of severe systemic disease at age ≤ 2 years of age

3. Must be ≥ 4 years of age, **AND**
4. Elelyso is administered by intravenous infusion by a healthcare professional and is covered under the medical benefit, **AND**
5. Elelyso will not be approved in combination with any other enzyme replacement therapy for Gaucher disease

Current body weight and requested dose regimen must be submitted for initial review and each recertification request

Elfabrio (pegunigalsidase alfa-iwxj)-Medical

1. Must be prescribed by or in consultation with an expert in genetics and management of Fabry disease, **AND**
2. Must be ≥18 years of age, **AND**
3. Must have a diagnosis of Fabry Disease confirmed as follows:

   Male patients:
   - Enzyme assay test in leukocytes, plasma, fibroblasts, or dried blood spots demonstrating complete deficiency or less than 3% of normal of alpha-galactosidase A activity (alpha-Gal A) **OR**
   - Documented GLA gene mutation by gene sequencing.

   Female patients:
   - Documented GLA gene mutation by gene sequencing is required for diagnosis, **AND**

4. Must have clinical symptoms of disease as noted below (except for classically affected males)

- Males: Classically affected of any age with complete deficiency or less than 3% of normal alpha-Gal A) activity treatment should begin treatment at time of diagnosis. Classically affected pediatric males typically begin treatment between 8–13 years of age.
- Atypically affected Males with residual alpha-Gal A activity (3-35% of normal mean): institute treatment if significant symptoms (see below) or evidence of progression of organ involvement
- Females (all ages): Monitor; institute treatment if significant symptoms (see below) or evidence of progression of organ involvement

Symptoms or physical findings of Fabry disease:

- Angiokeratomas: characteristic lysosomal disease skin rashes
- Hypohidrosis: decreased sweating
- Acroparesthesia: neuropathic pain in the hands and feet
- Cornea verticillata and characteristic corneal and lenticular opacities
- Diarrhea, abdominal pain, nausea, vomiting, flank pain, heat and cold intolerance, vertigo, tinnitus, diplopia, fatigue.
- Long term consequences include cardiac disease (including hypertrophic cardiomyopathy), arrhythmias, progressing renal disease (proteinuria to end stage renal disease) and stroke, **AND**

5. Must have experienced serious side effects or drug failure to Galafold (migalastat) except in the following circumstances:
   - Patients with severe, classical phenotype who demonstrate no alpha galactosidase activity **OR** those who exhibit severe clinical Fabry disease symptoms (as previously noted) where the provider has determined that Elfabrio is medically necessary.
   - Patients with estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m2 **OR** end-stage renal disease (ESRD)
   - Patients who do not have an amenable GLA gene mutation for treatment with Galafold based on the human embryonic kidney (HEK) 293 assay, **AND**
6. Elfabrio must be used as monotherapy and will NOT be covered in combination with Galafold (migalastat) or Fabrazyme. Please note - prior approval for any other Fabry disease specific treatment will be terminated upon approval of Elfabrio, **AND**
7. Current body weight and requested dose regimen must be submitted for initial review and each recertification request

   Recommended dosing: 1mg/kg body weight as an intravenous infusion every 2 weeks.

Fabrazyme (agalisidase beta) – Medical or Rx

1. Must be prescribed by or in consultation with an expert in genetics and management of Fabry disease, **AND**
2. Must be ≥ 2 years of age, **AND**
3. Must have a diagnosis of Fabry Disease confirmed as follows:

   Male patients:
   - Enzyme assay test in leukocytes, plasma, fibroblasts, or dried blood spots demonstrating complete deficiency or less than 3% of normal of alpha-galactosidase A activity (alpha-Gal A) **OR**
   - Documented GLA gene mutation by gene sequencing.

   Female patients:
   - Documented GLA gene mutation by gene sequencing is required for diagnosis, **AND**
4. Must have clinical symptoms of disease as noted below (except for classically affected males)
   - Males: Classically affected of any age with complete deficiency or less than 3% of normal alpha-Gal A) activity treatment should begin treatment at time of diagnosis. Classically affected pediatric males typically begin treatment between 8–13 years of age.
   - Atypically affected Males with residual alpha-Gal A activity (3-35% of normal mean): institute treatment if significant symptoms (see below) or evidence of progression of organ involvement

- Females (all ages): Monitor; institute treatment if significant symptoms (see below) or evidence of progression of organ involvement

Symptoms or physical findings of Fabry disease:

- Angiokeratomas: characteristic lysosomal disease skin rashes
- Hypohidrosis: decreased sweating
- Acroparesthesia: neuropathic pain in the hands and feet
- Cornea verticillata and characteristic corneal and lenticular opacities
- Diarrhea, abdominal pain, nausea, vomiting, flank pain, heat and cold intolerance, vertigo, tinnitus, diplopia, fatigue.
- Long term consequences include cardiac disease (including hypertrophic cardiomyopathy), arrhythmias, progressing renal disease (proteinuria to end stage renal disease) and stroke, **AND**

5. Must have experienced serious side effects or drug failure to Galafold (migalastat) except in the following circumstances:
   - Pediatric patients between the ages of 8 years old to less than 18 years old
   - Patients with severe, classical phenotype who demonstrate no alpha galactosidase activity **OR** those who exhibit severe clinical Fabry disease symptoms (as previously noted) where the provider has determined that Fabrazyme is medically necessary.
   - Patients with estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m2 **OR** end-stage renal disease (ESRD)
   - Patients who do not have an amenable GLA gene mutation for treatment with Galafold based on the human embryonic kidney (HEK) 293 assay, **AND**
6. Fabrazyme must be used as monotherapy and will NOT be covered in combination with Galafold (migalastat) or Elfabrio. Please note - prior approval for any other Fabry disease specific treatment will be terminated upon approval of Fabrazyme, **AND**
7. Current body weight and requested dose regimen must be submitted for initial review and each recertification request

Recommended dosing: 1mg/kg body weight as an intravenous infusion every 2 weeks.

Galafold (migalastat) –Rx

1. Must be prescribed by or in consultation with an expert in genetics and management of Fabry disease, **AND**
2. Must be ≥ 18 years of age, **AND**
3. Must have a diagnosis of Fabry Disease confirmed as follows:

   Male patients:
   - Enzyme assay test in leukocytes, plasma, fibroblasts, or dried blood spots demonstrating complete deficiency or less than 3% of normal of alpha-galactosidase A (alpha-Gal A) activity (classically affected, hemizygous males) **OR**
   - Documented GLA gene mutation by gene sequencing.

   Female patients:
   - Documented GLA gene mutation by gene sequencing is required for diagnosis, **AND**
4. Must have an amenable GLA gene mutation based on in vitro assay data (see manufacturer prescribing information for amenable GLA variants), **AND**
5. Must have clinical symptoms of disease as noted below (except for classically affected males)
   - Males: Classically affected of any age with complete deficiency or less than 3% of normal alpha-Gal A) activity treatment should begin treatment at time of diagnosis.
   - Atypically affected Males with residual alpha-Gal A activity (3-35% of normal mean): initiate treatment if significant symptoms (see below) or evidence of progression of organ involvement
   - Females (all ages): Monitor; institute treatment if significant symptoms (see below) or evidence of progression of organ involvement

Symptoms or physical findings of Fabry disease:
- Angiokeratomas: characteristic lysosomal disease skin rashes
- Hypohidrosis: decreased sweating
- Acroparesthesia: neuropathic pain in the hands and feet
- Cornea verticillata and characteristic corneal and lenticular opacities
- Diarrhea, abdominal pain, nausea, vomiting, flank pain, heat and cold intolerance, vertigo, tinnitus, diplopia, fatigue.
- Long term consequences include cardiac disease (including hypertrophic cardiomyopathy), arrhythmias, progressing renal disease (proteinuria to end stage renal disease) and stroke, **AND**

6. Must have an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73 m^2, **AND**
7. Galafold must be used as monotherapy and will NOT be covered in combination with Fabrazyme or Elfabrio. Please note: Prior approval for any other Fabry disease specific treatment will be terminated upon approval of Galafold.
8. Recommended dose of Galafold is 120mg orally once every other day at the same time of day on an empty stomach
9. Quantity limit of 14 capsules per 28 days
10. Initial approval will be for 1 year
11. Recertification every 2 years will require documentation of adequate renal function [(eGFR) of at least 30 mL/min/1.73 m2] **AND** a positive response to therapy for symptomatic individuals (via lab reports, progress notes documenting improvement in clinical symptoms) **AND** stability on the requested regimen.

Givlaari (givosiran) – Medical
1. Must be 18 years of age or older **AND** 2. Must be prescribed by a healthcare professional experienced in the diagnosis and management of acute hepatic porphyria such as a hepatologist, hematologist, gastroenterologist, neurologist **AND** 3. Must have a diagnosis of acute hepatic porphyria including one of the following 4 subtypes: Acute Intermittent Porphyria (AIP), Hereditary Coproporphyria (HCP), Variegate Porphyria (VP), ALA dehydratase-deficiency porphyria (ADP) confirmed by: i. Elevated levels of the porphyria precursor porphobilinogen (PBG) or aminolaevulinic acid (ALA) in urine or plasma within the previous year and/or ii. Genetic testing confirming a mutation consistent with AIP, HCP, VP, ADP, **AND** 4. Have active symptomatic disease with at least 2 documented porphyria attacks within the past 6 months prior to initiation, requiring hospitalization, urgent healthcare visits or intravenous Panhematin (hemin for injection) administration at home, **AND** 5. Factors or triggers contributing to acute hepatic porphyria attacks have been identified and addressed including but not limited to evaluation of hormonal (endocrine) factors, avoidance of alcohol, quitting smoking, dietary modifications, discontinuation of medications that may precipitate attacks of acute porphyria, when possible, **AND** 6. Givlaari will not be covered in the following scenarios as there is no data supporting safety and efficacy at this time a. Diagnosis of porphyria that is NOT confirmed as acute hepatic porphyria (such as porphyria cutanea tarda, hereditary erythropoietic porphyria, hepatoerythropoietic porphyria, erythropoietic protoporphyria) b. Impending liver transplantation or history of prior liver transplantation. Recipients of liver transplantation previously approved for Givlaari will not be permitted additional coverage of Givlaari after successful liver transplantation. c. Dose exceeding 2.5mg/kg once a month 7. Current body weight and requested dose regimen must be submitted for initial review and each recertification request. 8. Approval will be for 6 months at a time 9. Recertification after the initial 6 months of coverage requires documentation of all the following: a. Documentation supporting a reduction in frequency of acute hepatic porphyria attacks requiring hospitalization, urgent healthcare visits or intravenous hemin administration at home (for acute treatment and/or prophylaxis) from baseline levels, b. Patient has not experienced unacceptable or unmanageable toxicity such as anaphylactic reactions, hepatic toxicity, renal toxicity, or severe injection site reactions, **AND** c. Patient has not received a liver transplant <u>Recommended Dosing</u>: 2.5 mg/kg administered via subcutaneous injection once monthly. Dosing is based on actual body weight.
Kanuma (sebelipase alfa) – Medical
1. Patient must be followed by a physician experienced in metabolic disorders, **AND** 2. Must have a diagnosis of LAL deficiency confirmed by any combination of the following means: laboratory tests, imaging studies, genetic testing, and highly specific dried blood spot and either a or b: a. The clinical presentation should display an LDL-C concentration of 4.7 mmol/L or greater (or above the 95th percentile for age and sex). Based on review of family history, if disease is confirmed to be autosomal dominant no further testing is required, **OR** b. For individuals with unknown family history or recessive pattern, further evaluation should take place to see if any of the following exist. Individuals with at least 3 of these criteria should be tested by dry blood spot test for LAL activity (CPT code 82657). ○ ALT levels greater than 1.5 of the upper limits of normal (ULN)

- HDL-C levels less than 1.3 mml/L
- Body mass index of 30 kg/m2 or more
- Liver biopsy suggestive of microvesicular steatosis
- Hepatomegaly

3. Current body weight and requested dose regimen must be submitted for initial review and each recertification request

Recommended Dosing:

- For pediatric and adult patients with LAL deficiency, the recommended starting dose is 1mg/kg administered intravenously every other week.
- For patients with rapidly progressive LAL deficiency presenting within the first 6 months of life, the recommended starting dose is 1mg/kg administered intravenously once weekly. The dose may be increased up to 3mg/kg once weekly for patients who do not achieve clinical response with the lower dose.

Kuvan, Javygtor and generic sapropterin – Rx

1. Must be prescribed by a healthcare provider experienced in the management of PKU, **AND**
2. Patient must have a diagnosis of phenylketonuria (PKU) with hyperphenylalaninemia (HPA) **AND**
3. Patient must adhere to a phenylalanine (Phe) restricted diet
4. Current body weight and requested dose regimen must be submitted for initial review and each recertification request
5. All requests for brand Kuvan and Javygtor (initial and recertification) will require documentation of severe intolerance to generic sapropterin.
6. Initial approval will be for 2 months. Phe levels should be checked one week after initiation of therapy. If Phe levels do not decrease from baseline on a 10mg/kg/day dose, the dose maybe increased to 20mg/kg/day. If Phe levels do not decrease by at least 30% from baseline after 2 months, the patient is considered a non-responder and further therapy with Kuvan will not be authorized.
7. Recertification after the initial 2 months will occur every 2 years and require documentation of current body weight, requested dose regimen, continued adherence to Phe restricted diet and stability on requested therapy.

Recommended Dosing:

1. Kuvan/Javygtor / sapropterin is FDA approved for adults and children 1 month of age and older.
2. Maximum recommended dose is 20mg/kg/day.

Lamzede (velmanase alfa-tycv)-Medical

1. Prescribed by or in consultation with a provider knowledgeable in the management of alpha-mannosidosis **AND**
2. Must have a diagnosis of alpha-mannosidosis confirmed by enzyme assay demonstrating alpha-mannosidase activity <10% of normal activity **AND**
3. Must have mild or moderate alpha-mannosidosis
   a. Able to ambulate independently
   b. Absence of neurological manifestations
4. Lamzede will not be covered in the following circumstances:
   a. Patient has a history of a HSCT or bone marrow transplant
   b. Patient cannot walk without support
   c. Severe alpha-mannosidosis
5. Initial approval will be for 1 year and recertification will require documentation of a positive clinical response to Lamzede (i.e., improvement or stabilization in motor function, FVC, reduction in frequency of infections, etc.)

Recommended Dosing: 1 mg/kg (actual body weight) administered once every week as an intravenous infusion

Lenmeldy (atidarsagene autotemcel)-Medical

1. Must be prescribed by a provider who is knowledgeable in the management of metachromatic leukodystrophy (MLD).
2. Must have a diagnosis of MLD confirmed by **ALL** of the following:
   a. Biochemical Testing:
      i. Deficient Arylsulfatase-A (ARSA) enzyme activity in leukocytes (ARSA activity below the normal range in peripheral blood mononuclear cells or fibroblasts) **AND**
      ii. 24-hour urine collection showing elevated sulfatide levels; **AND**
   b. Molecular Testing:
      i. Identification of two pathogenic or novel *ARSA* allelles; **AND**
3. Must have a diagnosis of one of the following forms of MLD:
   a. Pre-symptomatic late infantile (PSLI) MLD defined by:
      i. Expected disease onset ≤ 30 months of age **AND**
      ii. Pre- symptomatic status defined as the absence of neurological signs and symptoms of MLD or physical exam findings limited to abnormal reflexes and/or clonus (excluding abnormal reflexes or abnormalities on brain magnetic resonance imaging and/or nerve conduction tests not associated with functional impairment (ex: no tremor, no peripheral ataxia))
   b. Pre-symptomatic early juvenile (PSEJ) MLD defined by:
      i. Expected disease onset >30 months and less than 7 years of age **AND**
      ii. Pre- symptomatic status defined as the absence of neurological signs and symptoms of MLD or physical exam findings limited to abnormal reflexes and/or clonus (excluding abnormal reflexes or abnormalities on brain magnetic resonance imaging and/or nerve conduction tests not associated with functional impairment (ex: no tremor, no peripheral ataxia))
   c. Early symptomatic early juvenile (ESEJ) MLD defined by:
      i. Disease onset >30 months and less than 7 years of age **AND**
      ii. Early symptomatic status defined as GMFC-MLD Level 0 with ataxia or GMFC-MLD Level 1 and IQ ≥ 85.
4. The patient must be eligible for an autologous hematopoietic stem cell transplant (HSCT) in accordance with the Autologous Hematopoietic (STEM) Cell Transplantation Medical Policy (Policy #: 7.02.03)
5. Individual does not have:
   a. Human immunodeficiency virus, hepatitis C virus, and/or hepatitis B virus positive
   b. Neoplastic disease
   c. Cytogenetic alteration typical of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML)
   d. End-organ dysfunction or other severe disease
   e. Allogeneic hematopoietic stem cell transplant (HSCT) in past 6 months or evidence of residual cells of donor origin
6. Lenmeldy is indicated for one-time single-dose intravenous use only and therefore will not be authorized for retreatment. Retreatment will be considered Experimental/Investigational when any FDA approved gene therapy, or any other gene therapy under investigation, has been previously administered
7. The minimum recommended dose of Lenmeldy is 2 to 11.8× 10^6 cells/mL (1.8 to 11.8 x 10^6 CD34+ cells/mL)
   a. Please refer to Lenmeldy FDA-approve prescribing information for complete dosage and administration instructions
   b. Lenmeldy is for autologous use only

8. Lenmeldy (atidarsagene autotemcel) is considered investigational when the above criteria are not met.
9. Lenmeldy (atidarsagene autotemcel) is considered investigational for all other indications, including late juvenile and adult forms of MLD.

Lumizyme (alglucosidase alfa) - Medical

1. Must have a diagnosis of Pompe Disease confirmed by identification of acid alpha-glucosidase activity deficiency from any tissue source and/or two confirmed GAA gene mutations or one confirmed GAA mutation with identification of acid alpha-glucosidase activity deficiency in a second sample
2. Patient must be followed by a physician experienced in metabolic disorders, **AND**
3. Patient has measurable signs of Pompe disease, such as impairment in pulmonary function or motor weakness **AND**
4. Patient must not have evidence of cardiac hypertrophy
5. Lumizyme will not be approved for use in combination with avalglucosidase alfa-ngpt (Nexviazyme)
6. Coverage will not be granted if patient previously failed avalglucosidase alfa-ngpt (Nexviazyme)
7. Documentation of baseline percent-predicted forced vital capacity (FVC) and 6-minute walk test (6MWT), current body weight and requested dose regimen must be submitted for initial review
8. Recertification will require documentation of response to therapy, as evidenced by an improvement or stabilization in percent-predicted FVC and/or 6-minute walk test (6MWT)

Recommended Dosing: 20mg/kg every 2 weeks

Mepsevii (vestronidase alfa-vjbk) – Medical

1. Patient must be followed by a physician experienced in metabolic disorders, **AND**
2. Must have a diagnosis of MPS VII, Sly Syndrome (mucopolysaccharidosis VII) confirmed by at least one of the following methods (i **OR** ii):
   i. Biochemical enzyme analysis for glucuronidase enzyme deficiency in white blood cells or cultured skin fibroblasts **OR**
   ii. Genetic testing
3. Must have urinary GAG excretion at least three-fold over the mean normal for age **AND**
4. Must have clinical signs of lysosomal storage disease including at least one of the following: enlarged liver and spleen, joint limitations, airway obstruction or pulmonary problems, heart valve abnormalities and limitation of mobility while still ambulatory **AND**
5. Current body weight and requested dose regimen must be submitted for initial review and each recertification request

Recommended Dosing: 4 mg/kg administered every 2 weeks by intravenous (IV) infusion

Miplyffa (arimoclomol)-Rx

1. Must be prescribed by or in consultation with a geneticist, neurologist, metabolic disorder specialist, or a physician who specializes in the treatment of Niemann-Pick disease type C (NPC) **AND**
2. Must be 2 years of age or older **AND**
3. Must have a diagnosis of NPC confirmed with documentation of biallelic pathogenic variants in either *NPC1* or *NPC2* identified by molecular genetic testing **AND**
4. Must have documentation of neurological manifestations of the disease (e.g., dysphagia, cognitive and/or speech impairment, progressive ataxia, dystonia, dysarthria, vertical supranuclear gaze palsy) **AND**
5. Must provide documentation of baseline body weight to verify FDA-approved dosing **AND**
6. For individuals weighing 15 kg or greater, must have serious side effects or drug failure with Aqneursa, or a medical reason why Aqneursa cannot be used **AND**
7. Prescriber must attest that the patient will use Miplyffa in combination with miglustat **AND**

8. Must provide documentation of the rescored 4-domain NPC Clinical Severity Scale (R4DNPCCSS) score at baseline (prior to initiating Miplyffa) which will be used to assess clinical response. (see Appendix for scale)
9. Miplyffa will not be authorized for any non-FDA approved indication **AND**
10. Miplyffa will not be authorized for use in combination with Aqneursa (levacetylleucine) as this combination has not been studied **AND**
11. Initial approval and recertification will be for 12 months at a time. Continued approval will require the patient has demonstrated stabilization and/or improvement in the rescored 4-domain NPC Clinical Severity Scale (R4DNPCCSS).
12. Quantity limit is 90 capsules/30 days.

Naglazyme (galsulfase)- Medical

1. Patient must be followed by a physician experienced in metabolic disorders, **AND**
2. Must have a diagnosis of Mucopolysaccharidosis IV confirmed by biochemical enzyme analysis for aryl sulfatase B enzyme deficiency or accumulation of dermatan sulfate lysosomal enzyme in cultured fibroblasts or isolated leukocytes, **AND**
3. Must have at least one of the following documented symptoms: coarse facial features, enlarged tongue, hepatosplenomegaly, hirsutism, prominent forehead, reduced stature and/or corneal clouding **AND**
4. Documentation of at least one of the following baseline tests:
   a. 6-minute walk test (6MWT) **OR**
   b. 3-minute stair-climb test
5. Recertification will require documentation of response to therapy, as evidenced by an improvement or stabilization in one of the above baseline tests.
6. Current body weight and requested dose regimen must be submitted for initial review and each recertification request

Recommended Dosing: 1 mg per kg given intravenously once weekly.

Nexviazyme (avalglucosidase alfa-ngpt)- Medical

1. Patient must be 1 year of age or older
2. Must have a diagnosis of late-onset Pompe Disease confirmed by identification of acid alpha-glucosidase activity deficiency from any tissue source and/or two confirmed GAA gene mutations or one confirmed GAA mutation with identification of acid alpha-glucosidase activity deficiency in a second sample
3. Patient must be followed by a physician experienced in metabolic disorders, **AND**
4. Patient has measurable signs of Pompe disease, such as impairment in pulmonary function or motor weakness **AND**
5. Patient must not have evidence of cardiac hypertrophy
6. Nexviazyme will not be approved for use in combination with alglucosidase alfa (Lumizyme)
7. Coverage will not be granted if patient previously failed alglucosidase alfa (Lumizyme)
8. Documentation of baseline percent-predicted forced vital capacity (FVC) and 6-minute walk test (6MWT), current body weight and requested dose regimen must be submitted for initial review
9. Recertification will require documentation of response to therapy, as evidenced by an improvement or stabilization in percent-predicted FVC and/or 6-minute walk test (6MWT)

Recommended Dosing: 20mg/kg for patients weighing 30kg (66 pounds) or more and 40mg/kg for those weighing less than 30 kg

nitisinone capsule, Nityr (nitisinone) and Orfadin (nitisinone)-Rx

1. Patient must be followed by a physician experienced in metabolic disorders, **AND**
2. Diagnosis confirmed by presence of succinylacetone in blood, urine, or dried blood spots (DBS), **AND**
3. Clinical features of disease such as: failure to thrive, fever, emesis, diarrhea, epistaxis, melena, developmental delay, hepatosplenomegaly, jaundice, ascites, purpura, clotting abnormalities, rickets, cirrhosis, renal disease/Fanconi syndrome, neurological crisis. Of note, clinical symptoms may be limited in newborns diagnosed during newborn screening, **AND**
4. Documentation of dietary restriction of tyrosine and phenylalanine is required, **AND**
5. Requests for Orfadin capsules will require documentation of serious side effects or drug failure of the equivalent generic product – nitisinone capsules.
6. Requests for Nityr tablets or Orfadin suspension will require documentation of severe intolerance or drug failure of the *preferred* product generic nitisinone capsules.
7. Current body weight and requested dose regimen must be submitted for initial review and each recertification request

Recommended Dosing:

- Initial dose should be 0.5mg/kg dosed twice daily. Dosage can be increased to 0.75mg/kg twice daily if succinylacetone is detectable 1 month after initiation
- Maximum dose should not exceed 1mg/kg twice daily

Nulibry (fosdenopterin) – Medical

1. Prescribed by or in consultation with a provider knowledgeable in the management of molybdenum cofactor deficiency (MoCD) Type A **AND**
2. Must have a diagnosis of molybdenum cofactor deficiency Type A confirmed by genetic testing that shows a mutation in the MOCS1 gene
3. Initial approval will be for 6 months, and recertification will require documentation of a positive clinical response to Nulibry (A positive response to therapy could be measured by urine and blood biomarkers (concentrations of s-sulfocysteine [SSC]), improvements in neurological function, gross motor function, developmental milestones, BMI, etc.)

Recommended Dosing:

- 0.9 mg/kg via IV infusion once daily for patients one year of age or older.
- For patients less than one year of age, the dose is based gestational age and body weight with patients less than 37 weeks old given an initial dose of 0.4mg/kg once daily, 0.7mg/kg once daily at month one and 0.9mg/kg once daily at month three.
- For patients 37 weeks or older the initial dose is 0.55mg/kg once daily, 0.75mg/kg once daily at month one and 0.9mg/kg once daily at month three.

Onpattro (patisiran) – Medical

1. Member is 18 years of age or older **AND**
2. Prescribed by specialist experienced in the diagnosis of hATTR amyloidosis such as hematologist-oncologist, neurologist, gastroenterologist, geneticist, or nephrologist **AND**
3. Diagnosis of hATTR amyloidosis with polyneuropathy **AND**
4. Documentation of a pathologic mutation in the transthyretin (TTR) gene (via genetic testing / DNA sequencing) **AND**
5. A baseline for one of the following diagnostic tests has been established (see below):
    i. Polyneuropathy disability (PND) score of IIIb or lower; **OR**
    ii. Documentation of baseline functional ambulation performance (FAP) stage of 1 or 2 **AND**
6. Must also have symptoms consistent with polyneuropathy attributed to hATTR and other causes of neuropathy have been excluded:
    - Peripheral sensorimotor polyneuropathy symptoms, such as: tingling or increased pain in the hands/feet/arms, loss of feeling in the hands/feet, numbness or tingling in the wrists, carpal tunnel syndrome, loss of ability to sense temperature or pain, difficulty with fine motor skills,

weakness/numbness/pain in the legs, difficulty walking, seizures, headaches, inability to perform activities of daily living (ADLs)
- Autonomic neuropathy symptoms such as: orthostasis, abnormal sweating, sexual dysfunction, recurrent urinary tract infection, dysautonomic symptoms of constipation, diarrhea, nausea, vomiting, anorexia, and early satiety **AND**

7. Patient has not been the recipient of an orthotopic liver transplant (OLT) **AND**
8. Must be administered by a healthcare professional **AND**
9. Onpattro must be used as monotherapy and will NOT be covered in combination with Tegsedi (inotersen) or any other polyneuropathy of hereditary transthyretin mediated amyloidosis (hATTR) disease specific therapy. Please note: Prior approval for any other polyneuropathy of hereditary transthyretin mediated amyloidosis (hATTR) specific treatment will be terminated upon approval of Onpattro, **AND**
10. Current body weight and requested dose regimen must be submitted for initial review and each recertification request.
11. Onpattro will not be approved for ATTR cardiomyopathy.
12. Initial approval for Onpattro will be for one year.
13. Continued approval beyond on year and recertification every two years will require:
    - Documentation of improvement **OR** stability of disease and symptoms with Onpattro (via lab reports, progress notes, neurologic exam, PND or FAP score.

Recommended Dosing: Less than 100kg: 0.3mg/kg every 3weeks /100kg or greater: 30mg every 3 weeks

Olpruva (sodium phenylbutyrate)-Rx

1. Must have a diagnosis of a urea cycle disorder diagnosed through newborn screening, DNA mutation analysis, enzyme analysis or other specialized testing, **AND**
2. Olpruva must be prescribed by physician experienced in the management of Urea Cycle Disorders (UCDs) and seen by a geneticist/metabolic specialist **AND** a nutritionist, **AND**
3. Must be used for a diagnosis of urea cycle disorder involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS) **AND**
4. Olpruva must be used with dietary protein restriction, **AND**
5. Olpruva will NOT be approved for the treatment of acute hyperammonemia in patients with Urea Cycle Disorders **AND**
6. All requests for Olpruva (initial and recertification) will require documentation of severe intolerance to generic sodium phenylbutyrate AND Pheburane.
7. Current body weight and height (or body surface area / BSA) and requested dose regimen must be submitted for initial review and each recertification request.
8. Quantity limit:
   a. 2G and 3G: 180 packets/30 days (1 kit)
   b. 4G, 5G ,6G, and 6.7G: 270 packets/30 days (1 kit)
9. Initial approval is for one year.

Recertification every 2 years will require documentation of continued dietary protein restriction, improvement in any clinical symptoms and stability on the requested therapy

Oxlumo (lumasiran)-Medical

1. Must be prescribed by or in consultation with a physician knowledgeable in the management of primary hyperoxaluria type 1 (PH1)
2. Must have a diagnosis of primary hyperoxaluria type 1 (PH1) confirmed by:
   a. Genetic testing that detects mutations of the alanine: glyoxylate aminotransferase (AGT) gene **OR**
   b. Liver biopsy demonstrating absent or significantly reduced AGT activity
3. Must have a metabolic screening that demonstrates
   a. Markedly increased urinary excretion of oxalate (i.e., greater than 0.7 mmol/1.73 m2 per day [90 mg/1.73 m2 per day]) **OR**

   b. Elevated oxalate:creatinine ratio in spot urine samples **OR**
   c. Plasma oxalate levels greater than or equal to 20 umol/L
      i. For individuals on hemodialysis, plasma oxalate should reflect pre-dialysis levels.
4. Documentation that the patient has made efforts to increase fluid intake to at least 3 L/m2 BSA per day.
5. Concurrent use of pyridoxine **OR** previous trial of at least 3 months of pyridoxine with no significant improvement observed (e.g., <30% reduction in urine oxalate concentration after at least 3 months of therapy)
6. Must not have had history of kidney or liver transplant
7. Must not be receiving peritoneal dialysis or combined peritoneal/hemodialysis
8. Current body weight and requested dose regimen must be submitted for initial review and each recertification request
9. Initial approval will be for 6 months
10. Recertification will be every 12 months and require documentation that the patient is tolerating therapy **AND**
    a. There was a reduction in urinary excretion of oxalate from baseline (improvement is reaching near normal (<1 mmol/1.73 m2 per day) urinary oxalate excretion) **OR**
    b. There was a reduction in plasma oxalate from baseline
       i. For individuals on hemodialysis, this improvement must reflect a pre-dialysis level.

Recommended Dosing:

Body Weight	**Loading Dose**	**Maintenance Dose (begin 1 month after the last loading dose)**
less than 10 kg	6 mg/kg once monthly for 3 doses	3 mg/kg once monthly
10 kg to less than 20 kg	6 mg/kg once monthly for 3 doses	6 mg/kg once every 3 months (quarterly)
20 kg and above	3 mg/kg once monthly for 3 doses	3 mg/kg once every 3 months (quarterly)

For patients on hemodialysis: Administer Oxlumo after hemodialysis if administered on dialysis days

Palynziq (pegvaliase-pqpz) – Rx

1. Must have a diagnosis of phenylketonuria (PKU) with hyperphenylalanemia (HPA) **AND**
2. Must be ≥ 18 years of age **AND**
3. Must be prescribed by a healthcare provider experienced in the management of PKU, **AND**
4. Must have documentation of elevated blood phenylalanine level (> 600 µmol/L) prior to treatment despite existing management with Kuvan/sapropterin (must be used in combination with dietary restrictions)
   a. For those with an inability to tolerate Kuvan/sapropterin **OR** those who are non-responders to Kuvan/sapropterin (defined as a decrease in phenylalanine levels of less than 30% from baseline after at least a 2-month trial with maximum dose for patient age), documentation of elevated blood phenylalanine level (> 600 µmol/L) will not be required

   Note: A recent PHE is required (within the past 30 days)
5. Palynziq must be used as monotherapy and will not be approved for use in combination with Kuvan / sapropterin
6. Maximum dose is 60mg subcutaneously once daily
7. Quantity limits apply: 2.5mg = 30/30; 10mg = 30/30; 20mg = 30/30
8. Initial approval is for 1 year to allow for dose titration and maintenance on 20mg SC once daily for at least 24 weeks and, if adequate response is not achieved, a dose increase to 40mg SC once daily. May increase to 60 mg once daily if blood phenylalanine control has not been achieved after 16 weeks on the 40-mg/day dosage.

9. Recertification after the initial approval and every 2 years thereafter will require documentation of achievement and maintenance of at least a 20% reduction in blood phenylalanine concentration from pre-treatment baseline or a blood phenylalanine concentration less than or equal to 600 µmol/L once maintenance dose is achieved.
10. Coverage will not be continued for patients who have not achieved a response (at least a 20% reduction in blood phenylalanine concentration from pre-treatment baseline or a blood phenylalanine concentration less than or equal to 600 µmol/L) after at least 16 weeks of continuous treatment with the maximum dosage of 60 mg once daily.

Recommended Dosing:

- Induction dose of 2.5mg subcutaneously (SC) once a week for 4 weeks then titrated, based on tolerability and blood phenylalanine concentrations, to maintenance dose of 20mg SC once a day over at least a 5-week period and continued for at least 24 weeks (refer to FDA approved package literature for dose titration schedule).
- After 24 weeks the dose may be increased to a maximum of 40mg SC once a day in patients who have not achieved a response (20% reduction in blood phenylalanine concentration from pre-treatment baseline or a blood phenylalanine concentration ≤ 600 µmol/L**)**.
- May increase to 60 mg once daily if blood phenylalanine control has not been achieved after 16 weeks on the 40-mg/day dosage. Discontinue therapy if adequate response is not achieved after 16 weeks of 60 mg once daily: MAX, 60 mg/day

Pombiliti (cipaglucosidase alfa-ATGA) - Medical

1. Must have a diagnosis of late-onset Pompe Disease confirmed by identification of acid alphaglucosidase activity deficiency from any tissue source and/or two confirmed GAA gene mutations or one confirmed GAA mutation with identification of acid alpha-glucosidase activity deficiency in a second sample
2. Must be at least 18 years old **AND** weigh ≥ 40 kg
3. Must be followed by a physician experienced in metabolic disorders, **AND**
4. Must have measurable signs of Pompe disease, such as impairment in pulmonary function or motor weakness **AND**
5. Must have an inadequate response to Lumizyme (alglucosidase alfa) or Nexviazyme (avalglucosidase alfa-ngpt)
6. Pombiliti must be used in combination with Opfolda (miglustat)
7. Documentation of baseline percent-predicted forced vital capacity (FVC) and 6-minute walk test (6MWT), current body weight and requested dose regimen must be submitted for initial review
8. Pombiliti will not be approved in combination with Lumizyme (alglucosidase alfa) or Nexviazyme (avalglucosidase alfa-ngpt)
9. Recertification will require documentation of response to therapy, as evidenced by an improvement or stabilization in percent-predicted FVC and/or 6-minute walk test (6MWT)

Ravicti (glycerol phenylbutyrate)-Rx

1. Must have a diagnosis of a urea cycle disorder diagnosed through newborn screening, DNA mutation analysis, enzyme analysis or other specialized testing, **AND**
2. Ravicti must be prescribed by physician experienced in the management of Urea Cycle Disorders (UCDs) and seen by a geneticist/metabolic specialist **AND** a nutritionist, **AND**
3. Must be used for a diagnosis of urea cycle disorder that cannot be managed by dietary protein restriction and/or amino acid supplementation alone, **AND**
4. Ravicti must be used with dietary protein restriction, **AND**
5. Ravicti will **NOT** be approved for the treatment of acute hyperammonemia in patients with Urea Cycle Disorders or for treatment of N-acetylglutamate synthase (NAGS) deficiency, **AND**
6. Current body weight and height (or body surface area / BSA) and requested dose regimen must be submitted for initial review and each recertification request.

7. Initial requests for Ravicti will require documentation of severe intolerance to generic sodium phenylbutyrate **AND** Pheburane.
8. Quantity limit is 525ml per 30 days
9. Initial approval is for one year.
10. Recertification every 2 years will require documentation of continued dietary protein restriction, improvement in any clinical symptoms and stability on the requested therapy.

Recommended Dosing:

- Recommended initial dosage in Phenylbutyrate-naïve patients is 4.5-11.2 mL/m²/day (5 to 12.4 g/m^2/day) given in 3 divided dosages via oral syringe or dosing cup, rounded up to the nearest 0.5mL, with a maximum of 17.5 mL/day. Should be taken with food.
- For patients switching from sodium phenylbutyrate to Ravicti, Patients should receive the same amount of phenylbutyric acid from the sodium phenylbutyrate dose. Calculate the dosage of Ravicti (mL) using the following equation
  a. Total daily dosage of Ravicti (mL) = total daily dosage of sodium phenylbutyrate tablets (g) x 0.86
  b. Total daily dosage of Ravicti (mL) = total daily dosage of sodium phenylbutyrate powder (g) x 0.81
- Neurotoxicity: (phenylacetate [PAA], the active moiety of Ravicti, may be toxic). Reduce dosage for symptoms of neurotoxicity such as: vomiting, nausea, headache, lightheadedness, somnolence, confusion, sleepiness or worsening of numbness, tingling, or burning in hands or feet are present in the absence of high ammonia or other intercurrent illnesses

Rivfloza (nedosiran)- Medical or Rx

1. Must be prescribed by or in consultation with a physician knowledgeable in the management of primary hyperoxaluria type 1 (PH1)
2. Must be ≥ 2 years of age
3. Must have a diagnosis of primary hyperoxaluria type 1 (PH1) confirmed by:
   a. Genetic testing that detects mutations of the alanine:glyoxylate aminotransferase (AGT) gene **OR**
   b. Liver biopsy demonstrating absent or significantly reduced AGT activity
4. Must have a metabolic screening that demonstrates
   a. Markedly increased urinary excretion of oxalate (i.e., greater than 1 mmol/1.73 m2 per day [90 mg/1.73 m2 per day]) **OR** elevated oxalate:creatinine ratio in spot urine samples **AND**
   b. Urinary excretion of glycolate
5. Documentation that the patient has made efforts to increase fluid intake to at least 3 L/m2 BSA per day.
6. Concurrent use of pyridoxine **OR** previous trial of at least 3 months of pyridoxine with no significant improvement observed (e.g., <30% reduction in urine oxalate concentration after at least 3 months of therapy)
7. Must have an eGFR ≥30 mL/min/1.73 m2
8. Must not have had history of kidney or liver transplant
9. Must not have clinical evidence of systemic oxalosis
10. Requests for Rivfloza (medical benefit only) will require documentation of an inability to self-inject. ****This applies to New Start AND Recertification requests (including new to plan) for all lines of business, except Medicare. Does NOT apply to Medicare B (Medicare Advantage)** For pediatric patients < 18 years of age, documentation must also include the inability of a caregiver to administer the medication
11. Rivfloza will not be approved in combination with Oxlumo
12. Current body weight and requested dose regimen must be submitted for initial review and each recertification request
13. Initial approval will be for 6 months

14. Recertification will require documentation that the patient is tolerating therapy and there was a reduction in urinary excretion of oxalate from baseline (improvement is reaching near-normal (<1 mmol/1.73 m2 per day) urinary oxalate excretion)
15. Quantity limit: 2 vials per 30 days / 1 prefilled syringe per 30 days

Strensiq (asfotase alfa)- Rx

1. Patient must be followed by a physician experienced in metabolic disorders, **AND**
2. Must have a diagnosis of perinatal/infantile- or juvenile-onset hypophosphatasia (HPP) with symptom onset at ≤ 12 years of age confirmed by both of the following (i and ii):
   i. Total serum ALP below the lower limit of normal for age (based upon laboratory-specific reference ranges).
      - If laboratory-specific reference ranges are not available, please refer to Table 1 (below) for ALP reference intervals, **AND**
   ii. The presence of elevated ALP substrate levels [increased serum pyridoxal 5'-phosphate (PLP) or urinary phosphoethanolamine (PEA)] **AND**
3. Must have evidence of clinical/radiographic symptoms including:
   a. Skeletal manifestations of HPP by radiographic evidence **OR**
   b. Presence of systemic complications (e.g., neurological, renal, respiratory, muscular, rheumatologic) **OR**
   c. Dental manifestations of HPP **OR**
   d. Family history of siblings or parents with HPP **AND**
4. Current body weight and requested dose regimen must be submitted for initial review and each recertification request, **AND**
5. Quantity limit: 1 vial per 28 days for all strength vials (18 mg/0.45 mL, 28 mg/0.7 mL, 40 mg/mL and 80 mg/0.8 mL)
   a. Upon each review and dose escalation request, the allowed quantity will be reviewed in accordance with FDA-approved weight-based dosing and, as such, will be limited to the minimum number of vials to obtain the appropriate weekly dose.
6. Initial approval and recertification will be for 6 months at a time.
   a. Clinical documentation must be submitted with each request and be within the previous 6 months.
   b. Recertification will require documentation of a positive response to therapy and stability on requested regimen (via lab reports and progress notes documenting improvement in any clinical / radiographic symptoms

- Recommended Dosing:

The recommended initial dose is 2mg/kg of body weight administered subcutaneously 3 times per week, or 1 mg/kg of body weight administered subcutaneously 6 times per week. The dose may be increased to 3mg/kg administered subcutaneously 3 times per week for insufficient efficacy in perinatal/infantile-onset HPP.

Sucraid (sacrosidase)- Rx

1. Patient must be followed by a physician experienced in the treatment of CSID, **AND**
2. Must have a diagnosis of congenital sucrase-isomaltose deficiency (CSID) confirmed by Small Bowel Biopsy with Disaccharidase Enzyme Testing (definitive test for diagnosing CSID).
   a. For individuals where invasive procedure is contraindicated, diagnosis can be confirmed by a positive sucrose breath test [carbon-13 (^{13}C) sucrose breath test]. Documentation of this contraindication is required.
   b. A sucrose hydrogen breath test alone is not enough to confirm the diagnosis. The sucrose hydrogen breath test is not specific for identifying CSID since other gastrointestinal conditions can also produce a positive hydrogen breath test.
3. Treatment will not be authorized as part of a therapeutic trial to confirm diagnosis

Recommended Dosing:

- Sucraid is FDA-approved for patients ≥5 months of age
- Adult dosage: 17,000 units with each meal or snack
- Children weighing > 15kg: 17,000 taken with each meal or snack
- Children weighing 15kg or less: 8,500 units taken with each meal or snack

Tegsedi (inotersen) –Rx

1. Member is 18 years of age or older **AND**
2. Prescribed by specialist experienced in the diagnosis of hATTR amyloidosis such as hematologist-oncologist, neurologist, gastroenterologist, geneticist, or nephrologist **AND**
3. Diagnosis of hATTR amyloidosis with polyneuropathy **AND**
4. Documentation of a pathologic mutation in the transthyretin (TTR) gene (via genetic testing / DNA sequencing **AND**
5. A baseline of one of the following diagnostic tests has been established (see below):
   a. Polyneuropathy disability (PND) score of IIIb or lower; **OR**
   b. Documentation of baseline Familial Amyloid Polyneuropathy (FAP) stage of 1 or 2 **AND**
6. Must also have some symptoms consistent with polyneuropathy attributed to hATTR and other causes of neuropathy have been excluded:
   a. Peripheral sensorimotor polyneuropathy symptoms, such as: tingling or increased pain in the hands/feet/arms, loss of feeling in the hands/feet, numbness or tingling in the wrists, carpal tunnel syndrome, loss of ability to sense temperature or pain, difficulty with fine motor skills, weakness/numbness/pain in the legs, difficulty walking, seizures, headaches, inability to perform activities of daily living (ADLs)
   b. Autonomic neuropathy symptoms such as: orthostasis, abnormal sweating, sexual dysfunction, recurrent urinary tract infection, dysautonomic symptoms of constipation, diarrhea, nausea, vomiting, anorexia, and early satiety **AND**
7. Patient has not been the recipient of an orthotopic liver transplant (OLT) **AND**
8. Platelet count ≥ 100 x 10^9/L **AND**
9. Baseline urine protein to creatinine ratio (UPCR) of ≤ 1000 mg/g **AND**
10. Tegsedi will not be covered in the following situations as they are contraindicated:
    a. platelets count less than 100 x 10^9/L
    b. history of acute glomerulonephritis caused by Tegsedi **AND**
11. Tegsedi must be used as monotherapy and will NOT be covered in combination with Onpattro (patisiren) or any other polyneuropathy of hereditary transthyretin mediated amyloidosis (hATTR) disease specific therapy. Please note: Prior approval for any other polyneuropathy of hereditary transthyretin mediated amyloidosis (hATTR) specific treatment will be terminated upon approval of Tegsedi **AND**
12. Recommended dose is 284mg administered by subcutaneous injection once per week.
13. Quantity limit of 6ml per 28-day supply
14. *Please note* for applicable lines of business, a split-fill program will apply to new starts only. An override to bypass the split-fill program will be provided for existing users that have been maintained on Tegsedi
15. Initial approval will be for 6 months.
16. Continued approval beyond 6 months and recertification every two years will require the following:
    a. Lab report documenting platelet count ≥ 100 x 10^9/L **AND**
    b. Lab report documenting urine protein to creatinine ratio (UPCR) of ≤ 1000 mg/g **AND**
    c. Documentation of improvement **OR** stability of disease and symptoms with Tegsedi (via lab reports, progress notes, neurologic exam, PND or FAP score)

Note: TEGSEDI® will only be approved for patients who have currently been receiving TEGSEDI®. According to the manufacturer, Sobi Inc., effective 9/27/24, TEGSEDI® (inotersen) will no longer be

available to patients in the US. Those patients who are currently receiving TEGSEDI® should consult with their healthcare practitioner about a transition plan.

Additional Drug Information:

- Tegsedi contains a boxed warning regarding the risks of thrombocytopenia (may result in sudden and unpredictable thrombocytopenia that can be life-threatening) and glomerulonephritis (may result in dialysis-dependent renal failure and/or and treatment with an immunosuppressive medication). Additional laboratory monitoring is required per FDA approved labeling. Based on monitoring, Tegsedi may need to be interrupted or discontinued

Polyneuropathy Disability (PND) score:

0 = No symptoms of neuropathy
I. = Sensory disturbances but preserved walking capability
II. = Impaired walking capacity but ability to walk without a stick or crutches
III.A. = Walking with the help of one stick or crutch
III.B.= Walking with the help of two sticks or crutches
IV. = Confined to a wheelchair or bedridden

Familial Amyloid Polyneuropathy (FAP) Stage:

0 = No symptoms of sensory or motor neuropathy
I. = Unimpaired ambulation; mostly mild sensory, motor, and autonomic neuropathy in the lower limbs
II. = Assistance with ambulation required mostly moderate impairment progression to the lower limbs, upper limbs, and trunk
III. = Wheelchair-bound or bedridden; severe sensory, motor, and autonomic involvement of all limbs

Vimizim (elosulfase alfa)-Medical

1. Patient must be followed by a physician experienced in metabolic disorders, **AND**
2. Must have a diagnosis of Morquio A Syndrome (Mucopolysaccharidosis IVA) confirmed by biochemical enzyme analysis for N-acetylgalactosamine-6-sulfate sulfatase (GALNS) activity using fibroblasts or leukocytes **AND**
3. Must have at least one of the following documented symptoms: short stature, abnormal gait, genu valgum, spinal abnormalities, chest abnormalities, joint abnormalities, respiratory compromise, cardiac valve abnormalities, muscular weakness, visual impairment, hearing loss, or dental abnormalities and oral health challenges **AND**
4. Must be ≥5 years of age.
5. Documentation of at least one of the following baseline tests:
   a. 6-minute walk test (6MWT) **OR**
   b. 3-minute stair-climb test
6. Recertification will require documentation of response to therapy, as evidenced by an improvement or stabilization in one of the above baseline tests.
7. Current body weight and requested dose regimen must be submitted for initial review and each recertification request

Recommended Dosing: 2 mg/kg given intravenously over a minimum range of 3.5 to 4.5 hours, based on infusion volume, once every week

VPRIV (velaglucerase alfa) – Medical

1. Prescribed by or in consultation with a physician knowledgeable in the management of Gaucher disease, **AND**
2. Must have a confirmed diagnosis of Gaucher disease (see Diagnosis section below for requirements), **AND**
   a. **Adults: Type 1 (nonneuronopathic)** Gaucher disease confirmed by:

- Biochemical assay of glucocerebrosidase activity in white blood cells (WBCs) or skin fibroblasts less than or equal to 30% **OR**
- Genotype mutation of two mutant alleles of the glucocerebrosidase gene **AND**
- Symptomatic manifestations of the disease
  - Skeletal disease as demonstrated by radiological evidence of joint deterioration, pathological fracture, osteopenia, avascular necrosis, osteosclerosis, marrow infiltration, lytic lesions, or Erlenmeyer flask deformity) **OR**
  - Hemoglobin ≤11.5 for females and ≤12.5 g/dl for males (or 1.0 g/dL below the lower limit of normal for age and sex), platelet count <= 60,000 mm^3, spleen > 15 times normal size, liver > 2.5 times normal size.

b**. Children Type 1 (nonneuronopathic):** less than 18 years of age with Type 1 Gaucher disease confirmed by:
- Biochemical assay of glucocerebrosidase activity in WBC's or skin fibroblasts is less than or equal to 30%. **OR**
- Genotype mutation of two mutant alleles of the glucocerebrosidase gene **AND**
- Symptomatic manifestations of the disease
  - Abdominal or bone pain, delayed growth, impaired psychomotor development, fatigue, exertional limitations, marrow infiltration, organomegaly, weakness and cachexia.

c. **Adults and Children Type III (neuronopathic):** Enzyme replacement therapy is considered off-label for this diagnosis; however, consideration will be given for the following scenarios in which ERT has been shown to be beneficial for hematological and visceral disease
- Individuals with chronic (not acute) neuronopathic Gaucher disease type 3
- Siblings of individuals with chronic neuronopathic Gaucher disease who have proven diagnosis
- Individuals with high-risk genotypes: L444P/L444P (c.1448T>C homozygote), D409H/D409H (c.1342G>C homozygote), L444P/D409H (c.1448T>C/c.1342G>C heterozygote)
- Onset of severe systemic disease at age ≤ 2 years of age

3. Must be ≥ 4 years of age, **AND**
4. VPRIV is administered by intravenous infusion by a healthcare professional and is covered under the medical benefit, **AND**
5. Commercial, Exchange and SafetyNet (Medicaid Managed Care, HARP, CHP, Essential Plan) lines of business: Requests for VPRIV, for NEW STARTS, AND EXISTING USERS at the time of recertification, will require documentation of serious side effects or drug failure with Elelyso (taliglucerase alfa). Medicare lines of business: Requests for VPRIV, for NEW STARTS ONLY, will require documentation of serious side effects or drug failure with Elelyso.
6. Current body weight and requested dose regimen must be submitted for initial review and each recertification request

Vyndaqel (tafamidis meglumine) and Vyndamax (tafamidis) –Rx

1. The patient must be 18 years of age or older **AND**
2. The medication must be prescribed by or in consultation with a physician who specializes in the treatment of amyloidosis, such as a cardiologist **AND**
3. The patient must have a diagnosis of cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) **AND**
4. The diagnosis must be confirmed by one the following:
   a. 99mTechnetium-labeled pyrophosphate cardiac imaging (nuclear scintigraphy) positive for TTR amyloid **OR**
   b. Amyloid deposits identified on cardiac biopsy **AND** presence of a variant TTR genotype and/or TTR precursor protein identification by molecular genetic testing (i.e., immunohistochemistry, scintigraphy, or mass spectrometry) or next-generation sequencing (NGS) **AND**

5. The patient must have a clinical history of heart failure classified as New York Heart Association Class I – III, with at least one prior hospitalization for heart failure **OR** in the absence of prior hospitalization must have clinical evidence of heart failure with signs/symptoms (such as shortness of breath, peripheral edema, ascites, elevated jugular pressure, etc.) requiring treatment with a diuretic for improvement **AND**
6. The patient must have evidence of cardiac involvement seen on echocardiography and/ or cardiac magnetic imaging, such as thickened left ventricle wall / septum **AND**
7. To effectively monitor treatment process and clinical improvement, documentation of the following clinical parameters is required prior to initiating therapy:
    a. Cardiac Biomarkers (NT-proBNP or troponin)
    b. TTR Protein Level (i.e., serum TTR)
    c. 6-Minute Walk Test
8. Recertification requirements
    a. First recertification (after initial approval) will require documentation of the following:
        i. A reduction in cardiac stress or damage, or improving function as evidenced by a decrease in NT-proBNP or troponin from baseline
        ii. Improvement or stabilization of the 6-Minute Walk test compared to baseline values
    b. Subsequent recertifications (after first recertification) will require documentation of the following:
        i. Continued reduction or stabilization of NT-proBNP or troponin (no increase in biomarker)
        ii. Continued improvement or stabilization of the 6-Minute Walk test compared to baseline values
9. Vyndaqel and Vyndamax must be used as monotherapy
    a. Vyndaqel and Vyndamax will NOT be covered for use in combination with acoramidis (Attruby) or vutrisiran (Amvuttra) for the treatment of ATTR-CM
        i. The concurrent use of transthyretin (TTR) stabilizers (e.g., tafamidis [Vyndamax/Vyndaqel] or acoramidis [Attruby]) and TTR silencers (e.g., vutrisiran [Amvuttra])) is considered not medically necessary due to the absence of clinical evidence demonstrating additional therapeutic benefit (e.g., additional reduction in mortality or hospitalization) and safety.
10. Vyndaqel and Vyndamax will NOT be covered in the following scenarios as there are no data supporting their safety and efficacy at this time:
    a. New York Heart Association Class IV heart failure
    b. Presence of primary (light chain) amyloidosis, secondary (AA) amyloidosis or any other non-ATTR amyloidosis
    c. Use in combination with Onpattro (patisiran), Tegsedi (inotersen), or Wainua (eplontersen)
    d. Prior liver transplant
11. Approved Dosage: See Prescribing Information
12. Quantity limit:
    a. Vyndamax: 30 capsules per 30 days
    b. Vyndaqel: 120 capsules per 30 days
13. Approval will be for 1 year at a time

Wainua (eplontersen) - Rx

1. Member is 18 years of age or older **AND**
2. Prescribed by specialist experienced in the diagnosis of hATTR amyloidosis such as hematologistoncologist, neurologist, gastroenterologist, geneticist, cardiologist or nephrologist **AND**
3. Diagnosis of hATTR amyloidosis with polyneuropathy **AND**
4. Documentation of a pathologic mutation in the transthyretin (TTR) gene (via genetic testing / DNA sequencing) **AND**
5. A baseline Polyneuropathy disability (PND) score of IIIb or lower
6. Must also have symptoms consistent with polyneuropathy attributed to hATTR and other causes of neuropathy have been excluded:

- Peripheral sensorimotor polyneuropathy symptoms, such as: tingling or increased pain in the hands/feet/arms, loss of feeling in the hands/feet, numbness or tingling in the wrists, carpal tunnel syndrome, loss of ability to sense temperature or pain, difficulty with fine motor skills, weakness/numbness/pain in the legs, difficulty walking, seizures, headaches, inability to perform activities of daily living (ADLs)
- Autonomic neuropathy symptoms such as: orthostasis, abnormal sweating, sexual dysfunction, recurrent urinary tract infection, dysautonomic symptoms of constipation, diarrhea, nausea, vomiting, anorexia, and early satiety **AND**

7. Patient has not been the recipient of an orthotopic liver transplant (OLT) **AND**
8. Wainua must be used as monotherapy and will NOT be covered in combination with Amvuttra (vutrisiran), Tegsedi (inotersen), Onpattro (patisiran) or any other polyneuropathy of hereditary transthyretin mediated amyloidosis (hATTR) disease specific therapy. Please note: Prior approval for any other polyneuropathy of hereditary transthyretin mediated amyloidosis (hATTR) specific treatment will be terminated upon approval of Wainua, **AND**
9. Initial approval for Wainua will be for one year.
10. Continued approval beyond on year and recertification every two years will require:
11. Documentation of improvement **OR** stability of disease and symptoms with Wainua (via lab reports, progress notes, neurologic exam, PND)
12. Quantity Limit: 1 pen per 30 days

Xenpozyme (olipudase alfa-rpcp)-Medical

1. Must be prescribed by or in consultation with a physician knowledgeable in the treatment of acid sphingomyelinase deficiency (ASMD) **AND**
2. Must have a diagnosis of ASMD with non-central nervous system (non-CNS) manifestations **AND**
   a. Must have documented deficiency, defined as < 10% enzyme compared to controls, of acid sphingomyelinase as measured in peripheral leukocytes, cultured fibroblasts, or lymphocytes **OR**
   b. Molecular genetic testing identifying a mutation in the *SMPD1* gene **AND**
3. Must not have type A ASMD (also known as Niemann-Pick disease type A). Note: clinical diagnosis consistent with ASMD type B or type A/B is acceptable **AND**
4. Baseline documentation of <u>at least one</u> of the following parameters will be required in order to verify clinical benefit upon recertification:
   a. Percent predicted diffusion capacity of the lungs for carbon monoxide (DLco).
      i. Note: considerations will be granted for other age-appropriate lung function tests in pediatric patients unable to perform this test
   b. Spleen volume
   c. Liver volume
   d. Platelet count
   e. Linear growth progression (as measured by height Z-score) (only applicable to pediatric patients < 18 years of age)
   f. Lyso-sphingomyelin levels

Initial and recertification approval will be granted for 12 months at a time. Recertification will require documentation of improvement from baseline in <u>at least one</u> of the parameters outlined in criterion #4a-f.

<u>Recommended dosing</u>:
Adults: Recommended starting dose is 0.1 mg/kg administered as an intravenous infusion.
Pediatrics: Recommended starting dose is 0.03 mg/kg administered as an intravenous infusion.
See Full Prescribing Information for the recommended dose escalation and maintenance dosage, dosage modifications to reduce the risk of adverse reactions, and preparation and administration instructions. Xenpozyme is administered via intravenous infusion every 2 weeks.

Xuriden (uridine triacetate) – Rx

1. Patient must be followed by a physician experienced in metabolic disorders **AND**

2. Diagnosis must be confirmed by:
    i. Genetic testing of the UMPS gene **OR**
    ii. Urine test that reveals very high amounts of orotic acid, with milder elevations of orotidine.
3. Must have at least one of the following documented symptoms (prior to treatment with uridine or Xuriden) attributed to the disease: Urinary orotic acid level significantly above the normal range, blood abnormalities (anemia, decreased white blood cell and neutrophil counts, etc.), urinary tract obstruction, developmental delays, failure to thrive, congenital malformations, and/or immune deficiencies **AND**
4. Must have trial and failure to the *preferred* product: over the counter (OTC) uridine, **AND**
5. Current body weight and requested dose regimen must be submitted for initial review and each recertification request, **AND**
6. Maximum daily dose is 8 grams per day according to the FDA approved labeling.
7. Quantity limit of 120 packets per 30 days, **AND**
8. *Please note:* for applicable lines of business, a split-fill program will apply to new starts only. An override to bypass the split-fill program will be provided for existing users that have been maintained on Xuriden
9. Initial approval will be for 6 months
10. Recertification every 2 years will require documentation of a positive response to therapy and stability on requested regimen (via lab reports and progress notes)

Recommended Dosing:

- Recommended dose for children and adults is 60mg/kg once a day.
- Increase to 120mg/kg (maximum 8 grams) for insufficient efficacy (e.g., urine orotic acid levels remaining above normal or increasing above the usual/expected range for the patient; lab values affected by orotic acid [red or white blood cell indices] worsening; worsening disease signs/symptoms)

See FDA approved labeling for 60mg/kg and 120mg/kg weight-based dosing tables

Yargesa/ Zavesca / miglustat –Rx

1. Must meet for ONE of the following diagnoses (A **OR** B):
    a. For a diagnosis of Gaucher disease
        i. Must be prescribed by or in consultation with a physician knowledgeable in the management of Gaucher disease, **AND**
        ii. Must have a confirmed diagnosis of Type 1 Gaucher disease (see Diagnosis section below for requirements)
            a. **Adults Type 1 (nonneuronopathic):** greater than 18 years of age with Type 1 Gaucher disease confirmed by i (a **OR** b) **AND** ii:
                i. One of the following:
                    1. Biochemical assay of glucocerebrosidase activity in white blood cells (WBCs) or skin fibroblasts less than or equal to 30% **OR**
                    2. Genotype mutation of two mutant alleles of the glucocerebrosidase gene
                ii. Symptomatic manifestations of the disease
                    1. Skeletal disease as demonstrated by radiological evidence of joint deterioration, pathological fracture, osteopenia, avascular necrosis, osteosclerosis, marrow infiltration, lytic lesions, or Erlenmeyer flask deformity) **OR**
                    2. Hemoglobin ≤11.5 for females and ≤12.5 g/dl for males (or 1.0 g/dL below the lower limit of normal for age and sex), platelet count <= 60,000 mm^3, spleen > 15 times normal size, liver > 2.5 times normal size.
            b. **Children Type 1 (nonneuronopathic):** less than 18 years of age with Type 1 Gaucher disease confirmed by i (a **OR** b) **AND** ii:
                i. One of the following:

1. Biochemical assay of glucocerebrosidase activity in WBC's or skin fibroblasts is less than or equal to 30%. **OR**
2. Genotype mutation of two mutant alleles of the glucocerebrosidase gene

ii. Symptomatic manifestations of the disease
1. Abdominal or bone pain, delayed growth, impaired psychomotor development, fatigue, exertional limitations, marrow infiltration, organomegaly, weakness and cachexia.

b. For a diagnosis of Niemann-Pick disease type C (NPC) the following criteria must be met:
i. Must be prescribed by or in consultation with a geneticist, neurologist, or metabolic disorder specialist, or a physician who specializes specializing in the treatment of Niemann-Pick disease type C (NPC) **AND**
ii. Must have a diagnosis of NPC confirmed with documentation biallelic pathogenic variants in either NPC1 or NPC2 identified by molecular genetic testing **AND**
iii. Must have neurological, psychiatric, and/or cognitive symptoms related to NPC **AND**
iv. Must provide documentation of disease severity status using an objective measurement scale at baseline (prior to initiating a miglustat product) which will be used to assess clinical response to therapy. (e.g., Niemann-Pick disease type C Clinical Severity Scale (NPCCSS)-17, rescored 4-domain NPC Clinical Severity Scale (R4DNPCCSS), fSARA) **AND**
v. Initial and recertification will be for 12 months at a time. Recertification will require the patient has demonstrated stabilization or improvement based on objective measurement scale provided upon initial approval (criterion iv) **AND**

2. Yargesa and Zavesca will not be authorized without documentation of serious side effects or drug failure to the AB rated generic equivalent miglustat **AND**
3. Yargesa, Zavesca / miglustat is approved for whom enzyme replacement therapy (taliglucerase alfa, imiglucerase, or velaglucerase alfa) is not a therapeutic option due to one or more of the following: allergy, hypersensitivity, or poor venous access **AND**
4. Yargesa, Zavesca / miglustat will not be approved for use in combination with enzyme replacement therapy (taliglucerase alfa, imiglucerase, or velaglucerase alfa) as this is considered investigational,
5. Quantity limit of 90 capsules per 30 days
   a. For a diagnosis of Gaucher disease, the maximum dose is 100 mg (1 capsule) three times a day
6. For a diagnosis of NPC, a quantity limit exception may be granted for up to 180 capsules per 30 days, to allow for maximum dose of 200 mg (2 capsules) three times a day

CODES:

Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract. CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.
Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

HCPCS:

J0225	Amvuttra
J0567	Brineura
J1786	Cerezyme
J0584	Crysvita
J1743	Elaprase
J3060	Elelyso
J0180	Fabrazyme
J0223	Givlaari

J2840	Kanuma
J0221	Lumizyme
J3397	Mepsevii
J1458	Naglazyme
J3490	Onpattro – Non-Facility
J0222	Onpattro – Facility
J1322	Vimizim
J3385	VPRIV

APPROVAL TIME PERIODS – INITIAL AND RECERTIFICATION REVIEWS:

1. Unless otherwise stated within the individual drug criteria, approval time periods are listed in the table below
2. Continued approval at time of recertification will require documentation that the drug is providing ongoing benefit to the patient in terms of improvement or stability in disease state or condition. Such documentation may include progress notes, imaging or laboratory findings, and other objective or subjective measures of benefit which support that continued use of the requested product is medically necessary. Also, ongoing use of the requested product must continue to reflect the current policy's preferred formulary [Recertification reviews may result in the requirement to try more cost-effective treatment alternatives as they become available (i.e., generics or other guideline-supported treatment options)] and the requested dose must continue to meet FDA approved or off-label/guideline supported dosing

Line of Business	Rx Initial approval	Rx Continued approval	Medical Initial approval	Medical Recert
Commercial / Exchange and SafetyNet (Medicaid, HARP, CHP, Essential Plan)	1 year (or as stated within individual drug policy) *Does not apply to Medicaid/HARP	2 years (or as stated within individual drug policy) *Does not apply to Medicaid/HARP	All sites of service – 2 years	All sites of service – 2 years
Medicare	Defined in Medicare Drug Policy	Defined in Medicare Drug Policy	All sites of service – 2 years	All sites of service – 2 years

Appendix:

Functional Scale for the Assessment and Rating of Ataxia (fSARA)

SARA Domain	Item	Modified Domain Score*
Domain 1: Gait	Normal, no difficulties in walking, turning, and walking tandem (up to one misstep allowed)	0
	Slight difficulties, only visible when walking 10 consecutive steps in tandem	1
	Clearly abnormal, tandem walking >10 steps not possible	1
	Considerable staggering, difficulties in half-turn, but without support	2
	Marked staggering, intermittent support of the wall required	2
	Severe staggering, permanent support of one stick or light support by one arm required	2
	Walking >10 m only with strong support (two special sticks or stroller or accompanying person)	3
	Walking <10 m only with strong support (two special sticks or stroller or accompanying person)	3
	Unable to walk, even supported	4
Domain	Normal, able to stand in tandem >10 s	0
	Able to stand with feet together without sway, but not in tandem for >10 s	1
	Able to stand with feet together for >10 s, but only with sway	1
	Able to stand for >10 s without support in natural position, but not with feet together	2

2: Stance	Able to stand for >10 s in natural position only with intermittent support	3
	Able to stand >10 s in natural position only with constant support of one arm	3
	Unable to stand for >10 s even with constant support of one arm	4
Domain 3: Sitting	Normal, no difficulties sitting >10 s	0
	Slight difficulties, intermittent sway	1
	Constant sway, but able to sit >10 s without support	2
	Able to sit for >10 s only with intermittent support	3
	Unable to sit for >10 s without continuous support	4
Domain 4: Speech Disturbance	Normal	0
	Suggestion of speech disturbance	1
	Impaired speech, but easy to understand	1
	Occasional words difficult to understand	2
	Many words difficult to understand	3
	Only single words understandable	4
	Speech unintelligible, anarthria	4

*Represents modified domain scores recommended by the Food and Drug Administration
Source: U.S. Food and Drug Administration. Drug Approval Package: Aqneursa. Integrated Review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2024/219132Orig1s000TOC.cfm Accessed on November 8, 2024.

Rescored 4-domain Niemann-Pick type C Clinical Severity Score (R4DNPCCSS)

Domain	Scoring Criteria		Score Range*
Ambulation	0 = Normal 1 = Clumsy 2 = Ataxic unassisted gait or not walking by 18 months 4 = Assisted ambulation or not walking by 24 months 5 = Wheelchair dependent		**0–5**
Fine Motor Skills	0 = Normal 1 = Slight dysmetria/dystonia (independent manipulation) 2 = Mild dysmetria/dystonia (requires little to no assistance, able to feed self without difficulty) 4 = Moderate dysmetria/dystonia (limited fine motor skills, difficulty feeding self) 5 = Severe dysmetria/dystonia (gross motor limitation, requires assistance for self-care activities)		**0–5**
Swallow	**Response Category**	**Rescored****	**0–5**
	Normal, no dysphagia	0	
	Cough while eating	1	
	Intermittent dysphagia with liquids	2	
	Intermittent dysphagia with solids	2	
	Intermittent dysphagia with liquids and solids	2	
	Dysphagia with liquids	3	
	Dysphagia with solids	3	
	Dysphagia with liquids and intermittent dysphagia with solids	3	
	Intermittent dysphagia with liquids and dysphagia with solids	3	
	Dysphagia with liquids and solids	3	
	Nasogastric tube or gastric tube for supplemental feeding	4	
	Nasogastric tube or gastric tube feeding only	5	
Speech	0 = Normal 1 = Mild dysarthria (easily understood) 2 = Severe dysarthria (difficult to understand) 3 = Non-verbal/functional communication skills for needs 5 = Minimal communication		**0–5**
R4DNPCCSS	Sum of all scores of the following domains with rescored Swallow domain: Ambulation, fine motor skills, swallow (rescored), speech		**0–20**

*A higher score equates to more severe clinical impairment
**[Note: for the swallowing domain the scoring categories were assigned a revised score value following the FDA's recommendation, this rescored version is present in this chart]

Sources:
Patterson MC, Lloyd-Price L, Guldberg C, et al. Validation of the 5-domain Niemann-Pick type C Clinical Severity Scale. Orphanet J Rare Dis. 2021;16(1):79. Published 2021 Feb 12. doi:10.1186/s13023-021-01719-2
Zevra. Arimoclomol for treatment of Niemann-Pick disease type C. Briefing document for the Food and Drug Administration Genetic Metabolic Disease Advisory Committee. Available at: https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-public-participation-information-august-2-2024-meeting-genetic-metabolic-diseases-advisory#event-materials. Accessed on November 8, 2024.

POLICY GUIDELINES:

1. Utilization Management are contract dependent and coverage criteria may be dependent on the contract renewal date. Additionally, coverage of drugs listed in this policy are contract dependent. Refer to specific contract/benefit language for exclusions.
2. Not all benefits allow coverage of healthcare professional administered drugs as part of their pharmacy benefit.
3. This policy is applicable to drugs that are included on a specific drug formulary (RX benefit only). If a drug referenced in this policy is non-formulary, please reference the Coverage Exception Evaluation Policy for All Lines of Business Formularies policy for review guidelines.
4. Clinical documentation must be submitted for each request (initial and recertification) unless otherwise specified (e.g., provider attestation required). Supporting documentation includes, but is not limited to, progress notes documenting previous treatments/treatment history, diagnostic testing, laboratory test results, genetic testing/biomarker results, and imaging.
   - Continued approval at time of recertification will require documentation that the drug is providing ongoing benefit to the patient in terms of improvement or stability in disease state or condition.
5. Supportive documentation of previous drug use must be submitted for any criterion that requires the trial of a preferred agent if the preferred drug is not found in claims history.
6. Dose and frequency should be in accordance with the FDA label or recognized compendia (for off-label uses). When services are performed in excess of established parameters, they may be subject to review for medical necessity.
7. This policy does not apply to Medicare Part D and D-SNP pharmacy benefits. The drugs in this policy may apply to all other lines of business including Medicare Advantage.
8. For members with Medicare Advantage, medications with a National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) will be covered pursuant to the criteria outlined by the NCD and/or LCD. NCDs/LCDs for applicable medications can be found on the CMS website at https://www.cms.gov/medicare-coverage-database/search.aspx. Indications that have not been addressed by the applicable medication's LCD/NCD will be covered in accordance with criteria determined by the Health Plan (which may include review per the Health Plan's Off-Label Use of FDA Approved Drugs policy). Step therapy requirements may be imposed in addition to LCD/NCD requirements.
9. For contracts where Insurance Law § 4903(c-1), and Public Health Law § 4903(3-a) are applicable, if trial of preferred drug(s) is the only criterion that is not met for a given condition, and one of the following circumstances can be substantiated by the requesting provider, then trial of the preferred drug(s) will not be required.
   - The required prescription drug(s) is (are) contraindicated or will likely cause an adverse reaction or physical or mental harm to the member;
   - The required prescription drug is expected to be ineffective based on the known clinical history and conditions and concurrent drug regimen;
   - The required prescription drug(s) was (were) previously tried while under the current or a previous health plan, or another prescription drug or drugs in the same pharmacologic class or with the same mechanism of action was (were) previously tried and such prescription drug(s) was (were) discontinued due to lack of efficacy or effectiveness, diminished effect, or an adverse event;
   - The required prescription drug(s) is (are) not in the patient's best interest because it will likely cause a significant barrier to adherence to or compliance with the plan of care, will likely worsen a

comorbid condition, or will likely decrease the ability to achieve or maintain reasonable functional ability in performing daily activities;
- The individual is stable on the requested prescription drug. The medical profile of the individual (age, disease state, comorbidities), along with the rational for deeming stability as it relates to standard medical practice and evidence-based practice protocols for the disease state will be taken into consideration.
- The above criteria are not applicable to requests for brand name medications that have an AB rated generic. We can require a trial of an AB-rated generic equivalent prior to providing coverage for the equivalent brand name prescription drug.

10. All requests will be reviewed to ensure they are being used for an appropriate indication and may be subject to an off-label review in accordance with our Off-Label Use of FDA Approved Drugs Policy (Pharmacy-32).
11. All utilization management requirements outlined in this policy are compliant with applicable New York State insurance laws and regulations. Policies will be reviewed and updated as necessary to ensure ongoing compliance with all state and federally mandated coverage requirements.

UPDATES:

Date:	**Revision:**
07/08/2025	Revised
05/19/2025	Revised
05/16/2025	Revised
05/08/2025	Reviewed / P&T Committee Approval
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04/10/2025	Revised
04/03/2025	Revised
03/06/2025	Revised
02/25/2025	Revised
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09/19/2024	Revised
09/13/2024	Revised
06/24/2024	Revised
06/11/2024	Revised
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03/13/2024	Revised
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2/8/21	Revised
1/12/2021	Revised
12/9/2020	Revised
10/2/2020	Revised
9/22/2020	Revised
6/9/2020	Revised
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9/2019	Revised
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3/19	Revised
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10/18	Revised
7/18	Revised
6/18	Revised
9/17	Committee Approval
6/17	Revised
11/16	Revised
10/16	Revised
7/16	Revised
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10/09	Reviewed
9/08	Revised

3/07	Created

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In addition to the full FDA approved prescribing information for each individual drug, the following references have been utilized in creating this policy and specific drug criteria:

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