

# Pharmacy Management Drug Policy

**SUBJECT: Inborn Errors of Metabolism (IEM) and Rare Genetic Diseases**

**POLICY NUMBER: Pharmacy-23**

**EFFECTIVE DATE: 3/1/2007**

**LAST REVIEW DATE: 11/22/2019**

*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. Medical or drug policies apply to commercial, SafetyNet, and Health Care Reform products only when a contract benefit for the specific service exists.*

## **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.

Contains policy criteria for the following products: Adagen, Aldurazyme, Brineura, Carbaglu, Cerdelga, Cerezyme, Cholbam, Crysvida, Elaprase, Eleyso, Fabrazyme, Galafold, Gamifant, Kanuma, Kuvan, Lumizyme, Mepsevii, miglustat, Naglazyme, nitisinone, Nityr, Onpattro, Orfadin, Palynziq, Ravicti, Revcovi, Strensiq, Sucraid, Tegsedi, Vimizim, VPRIV, Vyndaqel, Vyndamax, Xuriden, Zavesca

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

## **Disease Information, Drug Information and Clinical Policy Criteria:**

**Gaucher Disease:** Patients with Gaucher disease do not produce enough of an enzyme called glucocerebrosidase. Without this enzyme, a fatty substance called glucocerebroside (also called glucosylceramide) builds up in cells called macrophages. These cells can accumulate in the liver and spleen, causing the organs to become enlarged. Macrophages can also build up in the bone marrow, causing anemia (low red blood cell counts) and thrombocytopenia (low platelet counts). The basic goals of treatment are elimination or improvement of symptoms, prevention of irreversible damage, and improvement in the overall health and quality of life. An additional goal in children is optimization of growth.

**Diagnosis** – Confirmed diagnosis required for all drugs used to treat Gaucher disease:

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**

## Pharmacy Management Drug Policy

### Inborn Errors of Metabolic Diseases

- Hemoglobin  $\leq 11.5$  for females and  $\leq 12.5$  g/dl for males (or 1.0 g/dL below the lower limit of normal for age and sex), platelet count  $\leq 60,000$  mm<sup>3</sup>, 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 (applies to Elelyso, Cerezyme and VPRIV only):

- 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  $\leq 2$  years of age

#### 1. Elelyso (taliglucerase alfa) – Medical Benefit

##### Policy criteria:

Elelyso is an enzyme replacement therapy that is considered medically necessary for the treatment of Gaucher disease when ALL the following requirements have been met (a - f):

- a. Prescribed by or in consultation with a physician knowledgeable in the management of Gaucher disease, AND
- b. Must have a confirmed diagnosis of Gaucher disease (see Diagnosis section above for requirements), AND
- c. Must be  $\geq 4$  years of age, AND
- d. Elelyso is administered by intravenous infusion by a healthcare professional and is covered under the medical benefit, AND
- e. Elelyso will not be approved in combination with any other enzyme replacement therapy for Gaucher disease
- f. Current body weight and requested dose regimen must be submitted for initial review and each recertification request

#### 2. Cerezyme (imiglucerase) – Medical benefit

##### Policy criteria:

Cerezyme is an enzyme replacement therapy that is considered medically necessary for the treatment of Gaucher disease when ALL the following requirements have been met (a - g):

- a. Prescribed by or in consultation with a physician knowledgeable in the management of Gaucher disease, AND
- b. Must have a confirmed diagnosis of Gaucher disease (see Diagnosis section above for requirements), AND
- c. Must be  $\geq 2$  years of age, AND
- d. Cerezyme is administered by intravenous infusion by a healthcare professional and is covered under the medical benefit, AND

## Pharmacy Management Drug Policy

### Inborn Errors of Metabolic Diseases

- e. All requests for Cerezyme will be required to use Elelyso (taliglucerase alfa) except in the following situation:
  - i. 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.
  - ii. Individuals being treated with Cerezyme may be switched to Elelyso or VPRIV. Individuals previously treated on a stable dose of Cerezyme (imiglucerase) are recommended to begin treatment with VPRIV (velaglucerase alfa) or Elelyso (taliglucerase alfa) at that same dose, AND
- f. Cerezyme will not be approved in combination with any other enzyme replacement therapy for Gaucher disease
- g. Current body weight and requested dose regimen must be submitted for initial review and each recertification request

#### 3. VPRIV (velaglucerase alfa) – Medical benefit

##### Policy criteria:

VPRIV is an enzyme replacement therapy that is considered medically necessary for the treatment of Gaucher disease when ALL the following requirements have been met (a - f):

- a. Prescribed by or in consultation with a physician knowledgeable in the management of Gaucher disease, AND
- b. Must have a confirmed diagnosis of Gaucher disease (see Diagnosis section above for requirements), AND
- c. Must be  $\geq 4$  years of age, AND
- d. VPRIV is administered by intravenous infusion by a healthcare professional and is covered under the medical benefit, AND
- e. All requests for VPRIV will be required to use Elelyso (taliglucerase alfa) or provide documentation of serious side effects or drug failure to Elelyso
- f. Current body weight and requested dose regimen must be submitted for initial review and each recertification request

#### 4. Zavesca / miglustat – Pharmacy benefit

##### Policy criteria:

Zavesca (miglustat) is a substrate-reduction therapy that is considered medically necessary for the treatment of Type I Gaucher disease when ALL the following requirements have been met (a - f):

- a. Prescribed by or in consultation with a physician knowledgeable in the management of Gaucher disease, AND
- b. Must have a confirmed diagnosis of Type 1 (nonneuronopathic) Gaucher disease (see Diagnosis section above for requirements), AND
- c. Must be  $\geq 18$  years of age, AND
- d. 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
- e. 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, AND
- f. Zavesca will not be authorized without documentation of serious side effects or drug failure to the AB rated generic equivalent miglustat.

## Pharmacy Management Drug Policy

### Inborn Errors of Metabolic Diseases

#### 5. Cerdelga (eliglustat) – Pharmacy benefit

##### Policy Criteria:

Cerdelga is a substrate-reduction therapy that is considered medically necessary for the treatment of Type I Gaucher disease when ALL the following requirements have been met (a - g):

- a. Prescribed by or in consultation with a physician knowledgeable in the management of Gaucher disease, AND
- b. Must have a confirmed diagnosis of Type 1 (nonneuronopathic) Gaucher disease (see Diagnosis section above for requirements), AND
- c. Must be  $\geq$  18 years of age, AND
- d. Not covered in patients with pre-existing cardiac disease, long QT syndrome, and concomitant use of Class IA and Class III antiarrhythmics, AND
- e. Cerdelga will not be approved in combination with enzyme replacement therapy (taliglucerase alfa, imiglucerase, or velaglucerase alfa) as this is considered investigational, AND
- f. 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
- g. Dosing guidelines:
  - i. CYP2D6 EMs or IMs: approved dose is 84 mg orally **twice daily**
  - ii. CYP2D6 PMs: approved dose is 84 mg orally **once daily**
  - iii. CYP2D6 ultra-rapid metabolizers (URM) and CYP2D6 indeterminate metabolizers are excluded from coverage.
    1. CYP2D6 URMs may not achieve adequate concentrations of CERDELGA to achieve a therapeutic effect
    2. A specific dosage cannot be recommended for those patients whose CYP2D6 indeterminate
  - iv. The following drug interactions result in contraindication to Cerdelga and will not be covered:
    1. CYP2D6 EMs or IMs taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor.
    2. CYP2D6 IMs or PMs taking a strong CYP3A inhibitor.
  - v. Specific dosing information is listed in the Cerdelga package insert.
- h. 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.

**Fabry Disease:** Fabry disease (also called Anderson-Fabry disease) is an X-linked lysosomal storage disorder due to absent or significantly reduced alpha galactosidase activity which leads to the accumulation of a fatty substance – globotriaosylceramide (Gb3) – in a variety of cells and blood vessel walls throughout the body. The enzyme alpha galactosidase A is normally responsible for the breakdown of globotriaosylceramide. As the abnormal storage of this fatty compound increases with time, the channels of these vessels become narrowed, leading to decreased blood flow and decreased nourishment of the tissues normally supplied by these vessels. This abnormal process occurs in blood vessels throughout the body, particularly affecting vessels in the skin, kidneys, heart, brain and nervous system.

#### 1. Galafold (migalastat) – Pharmacy benefit

Galafold is indicated for the treatment of adults with a confirmed diagnosis of Fabry disease and an amenable alpha galactosidase A (GLA) gene variant based on *in vitro* assay data. This indication is approved under accelerated approval based on reduction in kidney interstitial capillary cell

## Pharmacy Management Drug Policy

### Inborn Errors of Metabolic Diseases

globotriaosylceramide (KIC GL-3) substrate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

#### Policy criteria:

Galafold is an oral pharmacologic chaperone that binds to and stabilizes specific mutant forms of the enzyme alpha-galactosidase, allowing its trafficking into the lysosome where it exerts its action and is considered medically necessary when ALL of the following requirements have been met (a – g):

a. Must be prescribed by or in consultation with an expert in genetics and management of Fabry disease, AND

b. Must be  $\geq 18$  years of age, AND

c. 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
- d. Must have an amenable GLA gene mutation based on in vitro assay data (see manufacturer prescribing information for amenable GLA variants), AND
- e. 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
- f. Must have an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73 m<sup>2</sup>, AND
- g. Galafold must be used as monotherapy and will NOT be covered in combination with Fabrazyme (agalidase beta). Please note: Prior approval for any other Fabry disease specific treatment will be terminated upon approval of Galafold.

#### Approval information:

- Initial approval will be for 1 year.
- Recertification every 2 years will require documentation of adequate renal function [(eGFR) of at least 30 mL/min/1.73 m<sup>2</sup>] 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.

#### Additional Drug Information:

# Pharmacy Management Drug Policy

## Inborn Errors of Metabolic Diseases

- Recommended dose of Galafold is 120mg orally once every other day at the same time of day on an empty stomach.
- A quantity limit of 14 capsules per 28 days will apply.

### 1. Fabrazyme (agalsidase beta) - Medical benefit

#### Policy Criteria:

Fabrazyme is an enzyme replacement therapy that provides affected patients with the deficient enzyme – alpha-galactosidase A (GLA) and is considered medically necessary if the following requirements have been met (a – g):

- a. Fabrazyme must be prescribed by or in consultation with an expert in genetics and management of Fabry disease, AND
- b. Must be ≥ 8 years of age, AND
- c. 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
- d. 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

- e. 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 m<sup>2</sup> 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
- f. Fabrazyme must be used as monotherapy and will NOT be covered in combination with Galafold (migalastat). Please note - prior approval for any other Fabry disease specific treatment will be terminated upon approval of Fabrazyme, AND

## Pharmacy Management Drug Policy

### Inborn Errors of Metabolic Diseases

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

Additional Drug Information:

Recommended dose is 1mg/kg body weight as an intravenous infusion every 2 weeks. There is no well-established maximum dose for the approved indication according to the prescribing information.

**Tyrosinemia Type 1:** Tyrosinemia type I results from deficiency of the enzyme fumarylacetoacetate hydrolase (FAH). Untreated tyrosinemia type I usually presents either in young infants with severe liver involvement or later in the first year with liver dysfunction and renal tubular dysfunction associated with growth failure and rickets.

#### **nitisinone capsule, Nityr (nitisinone) and Orfadin (nitisinone) – Pharmacy benefit**

Policy Criteria:

Nitisinone is a hydroxyphenyl-pyruvate dioxygenase inhibitor and is considered medically necessary for the treatment of hereditary tyrosinemia type 1 when the following requirements have been met (a - g):

- a. Patient must be followed by a physician experienced in metabolic disorders, AND
- b. Diagnosis confirmed by presence of succinylacetone in blood, urine or dried blood spots (DBS), AND
- c. 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
- d. Documentation of dietary restriction of tyrosine and phenylalanine is required, AND
- e. Requests for Orfadin capsules will require documentation of serious side effects or drug failure of the equivalent generic product – nitisinone capsules.
- f. Requests for Nityr tablets or Orfadin suspension will require documentation of severe intolerance or drug failure of the *preferred* product generic nitisinone capsules.
- g. Current body weight and requested dose regimen must be submitted for initial review and each recertification request

Additional Drug Information:

- Capsule dosage form: patients unable to swallow capsules may open capsules and suspend contents to a small amount of water, formula, or apple sauce for immediate administration
- 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

#### **Congenital Sucrase-Isomaltase Deficiency (CSID):**

##### **Sucraid (sacrosidase)-- Pharmacy benefit**

Policy Criteria:

Sucraid is considered medically necessary for members diagnosed with congenital sucrase-isomaltase deficiency within CSID when the following requirements have been met (a - c):

- a. Patient must be followed by a physician experienced in the treatment of CSID, AND
- b. Must have a diagnosis of CSID confirmed by Small Bowel Biopsy with Disaccharidase Enzyme Testing (definitive test for diagnosing CSID).

## Pharmacy Management Drug Policy

### Inborn Errors of Metabolic Diseases

- For individuals where invasive procedure is contraindicated, diagnosis can be confirmed by a positive sucrose breath test [carbon-13 (<sup>13</sup>C) sucrose breath test].
  - A sucrose hydrogen breath test is not specific for identifying CSID since other gastrointestinal conditions can also produce a positive hydrogen breath test.
- c. Treatment will not be authorized as part of a therapeutic trial to confirm diagnosis

#### Additional Drug Information:

- 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
- There is no well-established maximum dose for the approved indication according to the prescribing information.

**N-acetylglutamate Synthase deficiency (NAGs):** In people with N-acetylglutamate synthase deficiency, N-acetylglutamate is not available in sufficient quantities, or is not present at all. As a result, urea cannot be produced normally, and excess nitrogen accumulates in the blood in the form of ammonia. This accumulation of ammonia causes the neurological problems and other signs and symptoms of N-acetylglutamate synthase deficiency

#### **Carbaglu (carglumic acid) – Pharmacy benefit**

##### Policy Criteria:

Carbaglu is considered medically necessary for treatment of N-acetylglutamate Synthase deficiency when the following requirements have been met (a - c)

- a. Must have a confirmed diagnosis of N-acetylglutamate Synthase deficiency 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, AND
- b. Patient must be followed by a physician experienced in metabolic disorders, AND
- c. Patient must have a diagnosis of **acute** hyperammonemia due to the deficiency of the hepatic enzyme, N-acetylglutamate synthase (NAGs) AND during acute episode, must be receiving concomitant ammonia lowering therapies such as alternate pathway medications, hemodialysis, and dietary protein restriction OR  
Patient must have **chronic** hyperammonemia due to the deficiency of the hepatic enzyme, N-acetylglutamate synthase (NAGs)

##### Approval Information:

- Initial approval will be for one year
- Recertification every 2 years will require documentation of normalization of plasma ammonia levels, improvement in any clinical symptoms and stability on the requested therapy.
- Current body weight and requested dose regimen must be submitted for initial review and each recertification request

##### Additional Drug Information:

- Carbaglu is FDA-approved for neonates, infants, children, adolescents, and adults
- 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)
- Dosage for **maintenance** should be targeted for normal plasma ammonia level for age (usually less than 100mg/kg/day)
- Please note: Carbaglu should NOT be swallowed whole or crushed. Each 200mg tablet should be dissolved in a minimum of 2.5ml water and taken immediately. The remaining material inside the container should be rinsed with additional water and immediately administered to the patient



## Pharmacy Management Drug Policy

### Inborn Errors of Metabolic Diseases

- There is no well-established maximum dose for the approved indication according to the prescribing information.

**Pompe Disease:** Pompe disease is also called glycogen storage disease II, acid maltase deficiency, results from a deficiency in acid alpha-glucosidase (GAA). GAA deficiency has a classic infantile form presenting with hypertrophic cardiomyopathy and severe muscular hypotonia (decreased muscle tone or strength), as well as late-onset juvenile and adult form that typically presents without cardiac manifestations

#### **Lumizyme (alglucosidase alfa) - Medical benefit**

##### Policy Criteria:

Lumizyme is considered medically necessary for the treatment of Pompe Disease when the following requirements have been met (a-e):

- a. Must have a diagnosis of Pompe Disease confirmed by identification of acid alpha-glucosidase activity deficiency in cultured skin fibroblasts or peripheral blood lymphocytes or skin biopsy, or muscle, AND
- b. Patient must be followed by a physician experienced in metabolic disorders, AND
- c. Have at least one of the following documented symptoms:  
Readily observed evidence of glycogen storage (macroglossia, hepatomegaly, normal or increased muscle bulk), involvement of respiratory muscles manifesting as respiratory distress (eg, tachypnea), profound diffuse muscular hypotonia, AND
- d. Patient must not have evidence of cardiac hypertrophy, AND
- e. Current body weight and requested dose regimen must be submitted for initial review and each recertification request

##### Additional Drug Information:

- Lumizyme is FDA-approved for infants, children, adolescents, and adults
- Recommended dosage is 20mg/kg every 2 weeks
- There is no well-established maximum dose for the approved indication according to the prescribing information.

**Mucopolysaccharidosis (MPS I, II, IV, VI):** Mucopolysaccharidosis is characterized by defective activity of lysosomal enzymes, causing the accumulation of glucosaminoglycans (GAGs), resulting in cellular dysfunction and clinical abnormalities. The mucopolysaccharidosis subtypes are differentiated by the type and amount of accumulation.

#### **1. Aldurazyme (laronidase) - Medical benefit**

##### Policy Criteria:

Aldurazyme is considered medically necessary for the treatment of Hurler, Hurler-Scheie or Scheie form of MPS I when the following requirements have been met (a-e):

- a. Patient must be followed by a physician experienced in metabolic disorders, AND
- b. Must have a diagnosis of Hurler, Hurler-Scheie or Scheie form of MPS I confirmed by biochemical enzyme analysis for alpha-L-iduronidase enzyme deficiency in white blood cells or cultured skin fibroblasts, AND
- c. Have an affected 1<sup>st</sup> degree relative OR  
Have clinical symptoms of the disease such as: Valvular heart disease, cardiomyopathy, obstructive sleep apnea, restrictive lung disease, reactive airway disease, joint stiffness, joint contractures, joint pain, spinal deformities, corneal clouding, glaucoma, developmental delay, mental retardation, communicating hydrocephalus, hearing loss, hepatomegaly, inguinal/umbilical hernia and chronic infections, AND

# Pharmacy Management Drug Policy

## Inborn Errors of Metabolic Diseases

- d. Must be  $\geq 6$  months of age, AND
- e. Current body weight and requested dose regimen must be submitted for initial review and each recertification request

### Additional Drug Information:

- A boxed warning is included: Life-threatening anaphylactic reactions have been observed in some patients during ALDURAZYME infusions. Therefore, appropriate medical support should be readily available when ALDURAZYME is administered. Patients with compromised respiratory function or acute respiratory disease may be at risk of serious acute exacerbation of their respiratory compromise due to infusion reactions and require additional monitoring. Pretreatment is recommended prior to the infusion to reduce the risk of infusion reactions and may include antihistamines, antipyretics, or both. If infusion reactions occur, decreasing the infusion rate, temporarily stopping the infusion, or administering additional antipyretics and/or antihistamines may ameliorate the symptoms
- Recommended dosage is 0.58 mg/kg IV infusion once weekly
- There is no well-established maximum dose for the approved indication according to the prescribing information

## 2. Elaprase (idursulfase)-Medical benefit

### Policy Criteria:

Elaprase is considered medically necessary for treatment of Hunter syndrome (Mucopolysaccharidosis II) when the following requirements have been met (a-e):

- a. Patient must be followed by a physician experienced in metabolic disorders, AND
- b. 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
- c. Must have an affected 1<sup>st</sup> degree relative OR  
Must have 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
- d. Must be  $\geq 16$  months of age
- e. Current body weight and requested dose regimen must be submitted for initial review and each recertification request.

### Additional Drug Information:

- A boxed warning is included: Life-threatening anaphylactic reactions have been observed in some patients during ELAPRASE infusions. Therefore, appropriate medical support should be readily available when ELAPRASE is administered. Biphasic anaphylactic reactions have also been observed after ELAPRASE administration and patients who have experienced anaphylactic reactions may require prolonged observation. Patients with compromised respiratory function or acute respiratory disease may be at risk of serious acute exacerbation of their respiratory compromise due to infusion reactions and require additional monitoring.
- Risk of Hypersensitivity, Serious Adverse Reactions, and Antibody Development in Hunter Syndrome Patients with Severe Genetic Mutations: Hunter syndrome patients aged 7 years and younger with complete gene deletion, large gene rearrangement, nonsense, frame shift or splice site mutations experienced a higher incidence of hypersensitivity reactions, serious adverse reactions and anti-idursulfase antibody development
- Recommended dose is 0.5mg/kg IV infusion once a week.

## Pharmacy Management Drug Policy

### Inborn Errors of Metabolic Diseases

- There is no well-established maximum dose for the approved indication according to the prescribing information.

#### 3. Vimizim (elosulfase alfa)-Medical benefit

##### Policy Criteria:

Vimizim is considered medically necessary for the treatment of Morquio A Syndrome (Mucopolysaccharidosis IVA) when the following requirements have been met (a - e):

- a. Patient must be followed by a physician experienced in metabolic disorders, AND
- b. 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
- c. 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
- d. Must be  $\geq 5$  years of age.
- e. Current body weight and requested dose regimen must be submitted for initial review and each recertification request

##### Additional Drug Information

- A boxed warning is included: Life-threatening anaphylactic reactions have occurred in some patients during Vimizim infusions. Anaphylaxis, presenting as cough, erythema, throat tightness, urticaria, flushing, cyanosis, hypotension, rash, dyspnea, chest discomfort, and gastrointestinal symptoms (e.g., nausea, abdominal pain, retching, and vomiting) in conjunction with urticaria, have been reported to occur during Vimizim infusions, regardless of duration of the course of treatment. Closely observe patients during and after Vimizim administration and be prepared to manage anaphylaxis. Inform patients of the signs and symptoms of anaphylaxis and have them seek immediate medical care should symptoms occur. Patients with acute respiratory illness may be at risk of serious acute exacerbation of their respiratory compromise due to hypersensitivity reactions and require additional monitoring.
- The recommended dose is 2 mg/kg given intravenously over a minimum range of 3.5 to 4.5 hours, based on infusion volume, once every week

#### 4. Naglazyme (galsulfase)-Medical benefit

##### Policy Criteria:

Naglazyme is considered medically necessary for the treatment of Mucopolysaccharidosis VI (Maroteaux-Lamy syndrome) when the following requirements have been met (a - d):

- a. Patient must be followed by a physician experienced in metabolic disorders, AND
- b. 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
- c. 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
- d. Current body weight and requested dose regimen must be submitted for initial review and each recertification request

##### Additional Drug Information:

- Because of the potential for infusion reactions, patients should receive antihistamines with or without antipyretics prior to infusion. Despite routine pretreatment with antihistamines, infusion reactions,

## Pharmacy Management Drug Policy

### Inborn Errors of Metabolic Diseases

some severe, occurred in 30 of 55 patients treated with NAGLAZYME. Severe symptoms included angioneurotic edema, hypotension, dyspnea, bronchospasm, respiratory distress, apnea, and urticaria. The most common symptoms of infusion reactions included fever, chills/rigors, headache, rash, and mild to moderate urticaria. Nausea, vomiting, elevated blood pressure, retrosternal pain, abdominal pain, malaise, and joint pain were also reported. Initial reactions were observed as late as Week 55 of treatment.

- Recommended dose is 1 mg per kg given intravenously once weekly.

#### 5. Mepsevii (vestronidase alfa-vjbk) – Medical Benefit

##### Policy Criteria:

Mepsevii replaces the deficient enzyme, beta-glucuronidase (GUS) in MPS VII and is considered medically necessary for treatment of pediatric and adult patients with confirmed diagnosis of MPS VII, Sly Syndrome (mucopolysaccharidosis VII) when the following requirements have been met (a-e):

- a. Patient must be followed by a physician experienced in metabolic disorders, AND
- b. 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
- c. Must have urinary GAG excretion at least three-fold over the mean normal for age AND
- d. 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
- e. Current body weight and requested dose regimen must be submitted for initial review and each recertification request

##### Additional drug information:

- The recommended dose is 4 mg/kg administered every 2 weeks by intravenous (IV) infusion

**Urea Cycle Disorders (UCDs):** Urea Cycle disorders are genetic disorders caused by a mutation that results in a deficiency of 1 of the 6 enzymes in the urea cycle (a series of biochemical steps normally required to remove ammonia from the blood). The deficiency leads to accumulation of ammonia in the blood, which can cause brain damage, coma, or death.

#### Ravicti (glycerol phenylbutyrate)-Pharmacy Benefit

##### Policy Criteria:

Ravicti is considered medically necessary for the treatment of Urea Cycle Disorder when the following requirements have been met (a - g):

- a. Must have a diagnosis of a urea cycle disorder diagnosed through newborn screening, DNA mutation analysis, enzyme analysis or other specialized testing, AND
- b. 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
- c. 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
- d. Ravicti must be used with dietary protein restriction, AND
- e. 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

## Pharmacy Management Drug Policy

### Inborn Errors of Metabolic Diseases

- f. Current body weight and height (or body surface area / BSA) and requested dose regimen must be submitted for initial review and each recertification request.
- g. Quantity limit is 525ml per 30 days

#### Approval Information:

- 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.

#### Additional Drug Information:

- Recommended initial dosage in Phenylbutyrate-naïve patients is 4.5-11.2 mL/m<sup>2</sup>/day (5 to 12.4 g/m<sup>2</sup>/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
- Drug interactions of concern:
  - (1) Corticosteroids, valproic acid, or haloperidol: May increase plasma ammonia level. Monitor ammonia levels closely
  - (2) Probenecid: May affect renal excretion of metabolites of Ravicti, including PAGN and PAA

**Bile Acid Synthesis Disorders:** Bile acid synthesis (BAS) disorders are genetic disorders which cause enzyme deficiencies affecting infants, children, and adults. Inborn errors that interfere with the production of bile acid result in diminished production of regular bile acids as well as toxic intermediates. Complications from BAS include fat malabsorption, fat-soluble vitamin deficiency, neurological disease, liver disease, and cholestasis.

#### Policy Criteria:

##### **Cholbam (cholic acid)- Pharmacy benefit**

#### Policy Criteria:

Cholbam is considered medically necessary for the treatment of bile acid synthesis disorder when the following requirements have been met (a – g)

- a. Must have a diagnosis of bile acid synthesis disorder due to single enzyme defect (SED) OR
- b. Must be used as an adjunctive treatment of peroxisomal disorder (PD) including Zellweger spectrum disorder, in patients who exhibit manifestations of liver disease, steatorrhea, or complications from fat soluble vitamin absorption AND
- c. Diagnosis must be confirmed via gas chromatography-mass spectrometry analysis of the urine, which positively identifies elevated bile acids AND
- d. Must have elevated serum aminotransferases with normal serum gamma glutamyl transferase, AND
- e. Member must be seen by a hepatologist or gastroenterologist AND
- f. Must be at least 3 weeks old, AND
- g. Current body weight and requested dose regimen must be submitted for initial review and each recertification request.

## Pharmacy Management Drug Policy

### Inborn Errors of Metabolic Diseases

#### Approval Information:

- 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.
- 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.

#### Additional Drug Information:

- 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. Should be taken with food at least one hour before or 4 to 6 hours after taking a bile acid resin or aluminum-based antacid. For infants and children, capsule may be opened and mixed with formula, breast milk, or soft food.
- For patients with concomitant familial hypertriglyceridemia, the recommended dosage is 11 to 17 mg/kg (given in 1 or 2 divided doses).
- Bile Salt Efflux Pump (BSEP) Inhibitors (e.g., cyclosporine): Avoid concomitant use; if concomitant use is necessary, monitor serum transaminases and bilirubin

**Lysosomal Acid Lipase deficiency:** Lysosomal acid lipase (LAL) deficiency is a rare autosomal recessive genetic disorder in which patients have little to no LAL enzyme activity due to mutations in the Lipase A, Lysosomal Acid, Cholesterol Esterase (LIPA) gene which encodes the LAL enzyme. LAL deficiency results in the lysosomal accumulation of cholesterol esters and triglycerides (TG) in blood vessels and many tissues including the liver, spleen, and cardiovascular system. There are two major phenotypes of LAL deficiency which differ by rate of progression and severity. When LAL deficiency is diagnosed in infancy it is referred to as Wolman disease and represents the more rapidly progressing phenotype of the disease. These patients have a historic life expectancy of 3-6 months with a disease course characterized by liver failure, malabsorption, and growth failure. LAL deficiency presenting post-infancy is generally referred to as cholesteryl ester storage disease (CESD) and results in hepatic steatosis, hepatic fibrosis, and cirrhosis, and these patients are also at increased risk for accelerated atherosclerosis and cardiovascular disease.

#### **Kanuma (sebelipase alfa) – Medical benefit**

##### Policy Criteria:

Kanuma is considered medically necessary for the treatment of LAL deficiency when the following requirements have been met (a - c):

- a. Patient must be followed by a physician experienced in metabolic disorders, AND
- b. 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 i or ii:
  - i. 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
  - ii. 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 limit of normal (ULN)
    - HDL-C levels less than 1.3 mmol/L
    - Body mass index of 30 kg/m<sup>2</sup> or more
    - Liver biopsy suggestive of microvesicular steatosis

## Pharmacy Management Drug Policy

### Inborn Errors of Metabolic Diseases

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

#### Additional Drug Information:

- 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.

Hypersensitivity to Eggs or Egg Products: Consider the risks and benefits of treatment in patients with known systemic hypersensitivity reactions to eggs or egg products as Kanuma is produced in the egg whites of genetically engineered chickens

**Hypophosphatasia (HPP):** is a rare inherited metabolic disorder caused by mutations in the alkaline phosphatase (ALP) gene. These mutations affect bone and mineral metabolism. The disease is progressive and potentially life-threatening, leading to progressive and debilitating damage to vital organs, as well as bone deformity, pain and muscle weakness, respiratory failure and seizures. Its prevalence is estimated to be less than 20 patients per one million in the general population. Based on the age at onset of diagnosis and symptoms, 5 types of HPP have been identified: perinatal, infantile, childhood, adult, and odontophosphatasia. Clinical manifestations and severity of disease vary with age and type, ranging from the most severe cases occurring before birth and in infancy and less severe conditions in some adults. Mortality has been reported to be 50%-100% within the first year of life in the most severely affected patients.

#### **Strensiq (asfotase alfa)- Pharmacy benefit**

##### Policy Criteria:

Strensiq is considered medically necessary for the treatment of hypophosphatasia when the following requirements have been met (a - e):

- a. Patient must be followed by a physician experienced in metabolic disorders, AND
- b. Must have a diagnosis of perinatal/infantile- or juvenile-onset hypophosphatasia (HPP) with symptom onset at  $\leq 12$  years of age confirmed by both I and II:
  - 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
  - The presence of elevated ALP substrate levels [increased serum pyridoxal 5'-phosphate (PLP) or urinary phosphoethanolamine (PEA)] AND
- c. Must have evidence of clinical/radiographic symptoms including:
  - Skeletal manifestations of HPP by radiographic evidence OR
  - Presence of systemic complications (e.g., neurological, renal, respiratory, muscular, rheumatologic) OR
  - Dental manifestations of HPP OR
  - Family history of siblings or parents with HPP AND
- d. Current body weight and requested dose regimen must be submitted for initial review and each recertification request, AND
- e. Quantity limits:  
18mg/0.45ml vial= 10.8ml per 28 days

# Pharmacy Management Drug Policy

## Inborn Errors of Metabolic Diseases

28mg/0.7ml vial= 16.8ml per 28 days  
 40mg/ 1 ml vial= 24 ml per 28 days  
 80mg/ 0.8ml vial= 38.4 ml per 28 days

### Approval Information:

- Initial approval will be for 6 months.
- Recertification every 2 years 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)

### Additional Drug Information:

- 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.

Table 1:

Reference Intervals for Total ALP Activity in Serum or Plasma

Age	Male/Female Reference Intervals (ULN) <sup>a</sup>
<1 month	60-320
1-11 months	70-350
1-3 years	125-320
4-6 years	150-370
7-9 years	150-440
10-11 years	150-470/150-530
12-13 years	160-500/110-525
14-15 years	130-530/55-305
16-19 years	60-270/40-120
≥20 years	40-120

Adapted from ARUP laboratories. <sup>33,34</sup>

NOTE: children and adolescents have higher normal ALP activity compared with adults. Empiric historical references for the laboratory employed are preferred

ALP: alkaline phosphatase; ULN: upper limit of normal

**Hereditary Orotic Aciduria (HOA) or Orotic Aciduria Type I:** is an ultra-rare metabolic disorder affecting approximately 20 patients worldwide, usually diagnosed in infancy. It is caused by a defect in uridine-5'-monophosphate synthase (UMPS), an enzyme which converts orotic acid to UMP, a pyrimidine nucleotide. Patients are unable to synthesize pyrimidine nucleotides and accumulate orotic acid that otherwise would have been converted to UMP and excreted in the urine. Signs and symptoms include blood abnormalities (i.e. anemia, decreased white blood cell and neutrophil counts), urinary tract obstruction, developmental delays, failure to thrive, congenital malformations, and immune deficiencies

### Xuriden (uridine triacetate) – Pharmacy Benefit

#### Policy Criteria:

Xuriden is considered medically necessary for the treatment of Hereditary Orotic Acidura (HOA) when the following requirements have been met (a - g):

- Patient must be followed by a physician experienced in metabolic disorders AND
- Diagnosis must be confirmed by:
  - Genetic testing of the UMPS gene OR
  - Urine test that reveals very high amounts of orotic acid, with milder elevations of orotidine.
- 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



## Pharmacy Management Drug Policy

### Inborn Errors of Metabolic Diseases

obstruction, developmental delays, failure to thrive, congenital malformations, and/or immune deficiencies AND

- d. Must have trial and failure to the *preferred* product: over the counter (OTC) uridine, AND
- e. Current body weight and requested dose regimen must be submitted for initial review and each recertification request, AND
- f. Quantity limit of 120 packets per 30 days, AND
- g. *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

#### Approval Information:

- Initial approval will be for 6 months.
- Recertification every 2 years will require documentation of a positive response to therapy and stability on requested regimen (via lab reports and progress notes)

#### Additional Drug Information:

- 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
- The maximum daily dose is 8 grams per day according to the prescribing information.

**Ceroid Lipofuscinosis Type 2 (CLN2) / tripeptidyl peptidase 1 (TPP1) deficiency:** is a rare form of Batten disease. Batten disease includes a collection of hereditary neurological disorders that affect only 2-4 babies in every 100,000 live births. Only about 20 infants per year are born with CLN2 in the US. Individuals lack the enzyme TPP1, which causes developmental delays, muscle spasms, seizures, vision loss and other neurological symptoms. Symptoms typically begin between the ages of 2 to 4 and individuals gradually lose function, including speech and most cases are fatal before the age of 12 years.

#### **Brineura (cerliponase alfa) – Medical Benefit**

##### Policy Criteria:

Brineura is indicated to slow the loss of ability to walk or crawl (ambulation) in symptomatic pediatric patients 3 years of age and older with CLN2 / TPP1 deficiency and is considered medically necessary when the following requirements have been met (a - e):

- a. 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
- b. 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
- c. Must have a score of <6 on CLN2 clinical rating scale for motor and language function (see below for CLN2 rating scale), AND
- d. Must be ≥ 3 years of age AND
- e. 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).

##### Approval Information:

## Pharmacy Management Drug Policy

### Inborn Errors of Metabolic Diseases

- Initial approval will be for 6 months and requires a motor domain of the CLN2 Clinical Rating Scale score  $\geq 1$
- Continued approval beyond 6 months (see Approval Time Periods below 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:

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

**X-linked hypophosphatemia (XLH):** is a rare, hereditary, progressive disorder caused by a mutation in the phosphate regulating endopeptidase (PHEX) gene. XLH is characterized by renal phosphate wasting due to an overproduction of fibroblast growth factor 23 (FGF23), a hormone that promotes urinary phosphate excretion and suppresses renal production of active Vitamin D. In pediatric patients, XLH results in rickets/osteomalacia that leads to lower-extremity deformities, slowed growth, dental abnormalities and reduced height. Adults with XLH experience osteomalacia and often have severe joint, bone and tooth pain and an increased incidence of stress fractures/pseudofractures, particularly in the lower extremities.

#### **Crysvita (burosumab-twza) – Medical Benefit**

##### Policy Criteria:

Crysvita is 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 following requirements have been met (a - j):

- a. Member is 1 year of age or older AND
- b. Prescribed by specialist experienced in the treatment of metabolic bone disorders such as Endocrinologist, Nephrologist, Rheumatologist, Orthopedics AND
- c. Diagnosis confirmed by one of the following:
  - Elevated Serum fibroblast growth factor 23 (FGF23) level  $> 30$  pg/mL by Kainos assay or FGF23 Intact assay using full length active form (not C-terminal) OR
  - Molecular genetic testing - Identification of a hemizygous PHEX pathogenic variant in males, or a heterozygous PHEX pathogenic variant in females AND
- d. Documentation of serum phosphorus level below normal for age and gender (refer to lab report for reference ranges or refer to the table below). MUST provide recent lab report with reference ranges AND
- e. Clinical findings in progress notes and Radiographic features supporting XLH diagnosis:
  - Children: Rickets in wrists or knees, progressive bowing deformities of lower extremities, antero-medial rotational torsion of tibia, short stature; bone and joint pain; impaired physical function/gait disturbances, dental abnormalities (abscesses/tooth loss), family history of XLH.
  - Adults: Stress fractures of lower extremities, pseudofractures, Short stature, bowed legs, waddling gait, dental abnormalities (abscesses or tooth loss), hearing loss, evidence of enthesopathy (calcification of tendons, ligaments, and joint capsules), family history of XLH AND
- f. Adult (postpubescent, i.e. epiphyseal plate has fused) coverage is limited to symptomatic adults with spontaneous insufficiency fractures and/or disabling skeletal pain, impaired mobility, AND

# Pharmacy Management Drug Policy

## Inborn Errors of Metabolic Diseases

- g. Current body weight and requested dose regimen must be submitted for initial review and each recertification request, AND,
- h. Crysivita must be administered as a subcutaneous (SC) injection by a healthcare provider, AND
- i. Doses above 90mg will not be permitted for children or adults, AND
- j. Crysivita will NOT be covered in the following situations:
  - Severe renal impairment (eGFR < 30mL/min/1.73m<sup>3</sup>) or ESRD (end stage renal disease)
  - In combination with oral phosphate replacement or active vitamin D analogues (must be discontinued 1 week prior to initiation of Crysivita as use in combination is contraindicated)
  - Serum phosphorus levels above the upper limit of normal range.

### Approval Information:

Requests for recertification - documentation of the following is required (both a and b):

- a. Lab report(s) with reference range documenting normalization of serum phosphorus level. Serum phosphorus levels ≥ 5mg/dL require dose interruption per US Food and Drug Administration approved labeling and request must include physician treatment plan.
- b. Documentation in progress notes of improvement / stability in any clinical symptoms (for example: a reduction of bone pain, enhanced mobility, fracture reduction/healing, improvement of skeletal deformities).

### Additional Drug Information:

- a. Crysivita is available in a 10mg/mL, 20mg/mL and 30mg/mL single dose vial.
- b. Pediatric patients age 1 to less than 18 years of age – starting dose 0.8mg/kg of body weight rounded to nearest 10mg administered every 2 weeks. Dosage is adjusted no more frequently than every 4 weeks based on serum phosphorus levels. Maximum dose is 90mg every 2 weeks.
- c. 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.
- d. Quantity Guidelines: 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).

Fasting serum phosphorus (Phosphate, PO <sub>4</sub> ) 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.

## Pharmacy Management Drug Policy

### Inborn Errors of Metabolic Diseases

**Phenylketonuria (PKU):** is an inherited inability to metabolize phenylalanine due to a deficiency of phenylalanine hydroxylase (PAH) that causes brain and nerve damage with resulting intellectual disability if untreated.

#### **Kuvan (sapropterin) – Pharmacy benefit**

##### Policy Criteria:

Kuvan is considered medically necessary for the treatment of phenylketonuria (PKU) when the following requirements have been met (a -d):

- a. Must be prescribed by a healthcare provider experienced in the management of PKU, AND,
- b. Patient must have a diagnosis of phenylketonuria (PKU) with hyperphenylalaninemia (HPA) AND
- c. Patient must adhere to a phenylalanine (Phe) restricted diet
- d. Current body weight and requested dose regimen must be submitted for initial review and each recertification request

##### Approval Information:

- 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.
- 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.

##### Additional Drug Information:

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

#### **Palynziq (pegvaliase-pqpz) – Pharmacy Benefit**

Palynziq is a synthetic enzyme substitution therapy that substitutes for the deficient phenylalanine hydroxylase (PAH) enzyme, thereby reducing the blood phenylalanine concentration.

##### Policy Criteria

Palynziq is considered medically necessary for the treatment of PKU when the following requirements have been met (a - e):

- a. Must have a diagnosis of phenylketonuria (PKU) with hyperphenylalanemia (HPA) **AND**
- b. Must be  $\geq$  18 years of age **AND**
- c. Must be prescribed by a healthcare provider experienced in the management of PKU, **AND**
- d. Must have documentation of elevated blood phenylalanine level ( $> 600 \mu\text{mol/L}$ ) for 6 months prior to treatment despite existing management including both of the following (I and II)
  - I. Dietary restriction of phenylalanine **AND**
  - II. Trial of *preferred* product Kuvan (sapropterin) for 6 months (must be used in combination with dietary restrictions).  
Note: An exception to the 6-month trial of Kuvan is permitted as follows: Documentation that patient is a non-responder to Kuvan after at least a 2-month trial with maximum dose for patient age. Non-responder to Kuvan is defined as a decrease in phenylalanine levels of less than 30% from baseline.
- e. Palynziq must be used as monotherapy and will not be approved for use in combination with Kuvan

## Pharmacy Management Drug Policy

### Inborn Errors of Metabolic Diseases

#### Approval information:

- 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.
- Coverage of Palynziq after the initial approval will be for two years and 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.
- 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 40 mg once daily.

#### Additional Drug Information:

- 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  $\leq$  600 µmol/L).
- Therapeutic response may not be achieved until the patient is titrated to an effective maintenance dosage of Palynziq (20mg per day for at least 24 weeks or 40mg per day for at least 16 weeks.)
- Palynziq is a subcutaneous injection appropriate for self-administration and coverage is provided under the pharmacy benefit. Consideration for coverage under the medical benefit will require documentation of an inability to either self-administer Palynziq or to be administered by a caregiver.

Resource for phenylalanine unit conversion (mg/dL to umol/L OR umol/L to mg/dL):

<http://www.endmemo.com/medical/unitconvert/Phenylalanine.php>

**Transthyretin-mediated amyloidosis (ATTR):** is a rapidly progressing, life-threatening disorder caused by misfolding of the transthyretin (TTR) protein accumulating as amyloid fibrils and plaques in nerves, heart, or gastrointestinal tract. More than 95% of TTR circulating in the body is produced by the liver and is present in all human serum. Clinical presentation of ATTR may include a predominantly neurologic phenotype (formerly known as familial amyloid polyneuropathy or FAP), a predominantly cardiac phenotype (formerly known as familial cardiomyopathy), or both neurologic and cardiac effects. Most patients experience both neurologic and cardiac symptoms. In addition, other organ systems may be affected (e.g., gastrointestinal, renal, and ocular effects), particularly as the disease progresses.

Current treatments for ATTR aim to reduce or prevent abnormal TTR protein or stabilize the TTR protein and include:

- (1) Onpattro and Tegsedi indicated to treat polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR), and
- (2) Vyndaqel indicated to treat cardiomyopathy of transthyretin -mediated amyloidosis

#### **1. Onpattro (patisiran) – Medical Benefit**

Onpattro is a small interfering ribonucleic acid (siRNA) treatment. Onpattro silences a portion of RNA involved in causing hATTR. Prevention of abnormal TTR production by the liver is designed to reduce the accumulation of amyloid deposits in peripheral nerves; improving symptoms and helping patients better manage the condition.

## Pharmacy Management Drug Policy

### Inborn Errors of Metabolic Diseases

#### Policy criteria:

Onpattro is considered medically necessary for treatment of polyneuropathy of hereditary transthyretin mediated amyloidosis (hATTR) when the following requirements have been met (a through j):

- a. Member is 18 years of age or older **AND**
- b. Prescribed by specialist experienced in the diagnosis of hATTR amyloidosis such as hematologist-oncologist, neurologist, gastroenterologist, geneticist or nephrologist **AND**
- c. Diagnosis of hATTR amyloidosis with polyneuropathy **AND**
- d. Documentation of a pathologic mutation in the transthyretin (TTR) gene (via genetic testing / DNA sequencing) **AND**
- e. 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**
- f. 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**
- g. Patient has not been the recipient of an orthotopic liver transplant (OLT) **AND**
- h. Must be administered by a healthcare professional **AND**
- i. 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**
- j. Current body weight and requested dose regimen must be submitted for initial review and each recertification request.

#### Approval Information:

- Initial approval for Onpattro will be for one year.
- Continued approval beyond one 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).

#### Additional Drug Information:

- FDA approved dose:
  - Less than 100kg: 0.3mg/kg every 3 weeks
  - 100kg or greater: 30mg every 3 weeks

## 2. Tegsedi (inotersen) – Pharmacy Benefit

Tegsedi is an antisense oligonucleotide that works by targeting TTR messenger RNA to reduce the production of serum transthyretin (TTR) protein and TTR protein deposits in tissues, thus reducing the symptoms of polyneuropathy.

#### Policy criteria:

Tegsedi is considered medically necessary for treatment of polyneuropathy of hereditary transthyretin mediated amyloidosis (hATTR) when the following requirements have been met (a through l):

## Pharmacy Management Drug Policy

### Inborn Errors of Metabolic Diseases

- a. Member is 18 years of age or older **AND**
- b. Prescribed by specialist experienced in the diagnosis of hATTR amyloidosis such as hematologist-oncologist, neurologist, gastroenterologist, geneticist or nephrologist **AND**
- c. Diagnosis of hATTR amyloidosis with polyneuropathy **AND**
- d. Documentation of a pathologic mutation in the transthyretin (TTR) gene (via genetic testing / DNA sequencing **AND**
- e. A baseline of 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 Familial Amyloid Polyneuropathy\_(FAP) stage of 1 or 2 **AND**
- f. Must also have some 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**
- g. Patient has not been the recipient of an orthotopic liver transplant (OLT) **AND**
- h. Platelet count  $\geq 100 \times 10^9/L$  **AND**
- i. Baseline urine protein to creatinine ratio (UPCR) of  $\leq 1000$  mg/g **AND**
- j. Tegsedi will not be covered in the following situations as they are contraindicated:
  - platelet count less than  $100 \times 10^9/L$
  - history of acute glomerulonephritis caused by Tegsedi **AND**
- k. 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**
- l. *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

#### Approval information:

- Initial approval will be for 6 months.
- Continued approval beyond 6 months and recertification every two years will require the following:
  - Lab report documenting platelet count  $\geq 100 \times 10^9/L$  **AND**
  - Lab report documenting urine protein to creatinine ratio (UPCR) of  $\leq 1000$  mg/g **AND**
  - Documentation of improvement OR stability of disease and symptoms with Tegsedi (via lab reports, progress notes, neurologic exam, PND or FAP score)

#### Additional Drug Information:

- Recommended dose is 284mg administered by subcutaneous injection once per week.
- 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

# Pharmacy Management Drug Policy

## Inborn Errors of Metabolic Diseases

### 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

IIIA. = Walking with the help of one stick or crutch

IIIB. = 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

### **3. Vyndaqel (tafamidis meglumine) and Vyndamax (tafamidis) – Pharmacy Benefit**

Vyndaqel and Vyndamax are selective stabilizers of transthyretin (TTR) indicated for the treatment of the cardiomyopathy of wild type (ATTRwt-CM; associated with aging) or hereditary (hATTR-CM) transthyretin-mediated amyloidosis in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization. Accumulation of amyloid fibrils/deposits in the heart ventricles ultimately causes the myocardium to become stiff and/or weak, leading to heart failure.

### Policy Criteria:

Vyndaqel and Vyndamax are considered medically necessary for the treatment of wild type (ATTRwt-CM) or hereditary (hATTR-CM) transthyretin-mediated amyloidosis when the following requirements have been met (a – g):

- a. Member is 18 years of age or older, AND
- b. Prescribed by a physician who specializes in the treatment of amyloidosis, such as a cardiologist AND
- c. Must have a diagnosis 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
- d. Evidence of cardiac involvement seen on echocardiography and/ or cardiac magnetic imaging, such as thickened left ventricle wall / septum, AND
- e. Diagnosis confirmed by one the following:
  - i. <sup>99m</sup>Techneium-labeled pyrophosphate cardiac imaging (nuclear scintigraphy) positive for TTR amyloid, OR
  - ii. 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)
- f. Baseline measurement of 6 minute-walk-test
- g. Vyndaqel and Vyndamax will NOT be covered in the following scenarios as there are no data supporting their safety and efficacy at this time:
  - New York Heart Association Class IV heart failure
  - Presence of primary (light chain) amyloidosis, secondary (AA) amyloidosis or any other non-ATTR amyloidosis.
  - Use in combination with medications used to treat polyneuropathy of hereditary transthyretin mediated amyloidosis such as Onpattro (patisiran) or Tegsedi (inotersen)
  - Use of Vyndaqel and Vyndamax in combination
  - Prior liver transplant



## Pharmacy Management Drug Policy

### Inborn Errors of Metabolic Diseases

#### Approval Information:

- Approval will be for one year at a time.
- Yearly recertification requirements:
  - Patient continues to meet the initial policy criteria
  - Improvement or stabilization of the 6-minute-walk-test compared to baseline values
  - Progress notes documenting stability on therapy such as slowing of clinical decline and/or decrease in number of hospitalizations

#### Additional Drug Information:

- Recommended dosing: Vyndaqel 80mg (taken as four 20mg capsules) once daily; Vyndamax 61mg capsule once daily. Vyndaqel 80mg and Vyndamax 61mg are considered to have the same clinical efficacy but are NOT interchangeable on a per mg basis.

**Hemophagocytic lymphohistiocytosis (HLH):** is a rare life-threatening disorder characterized by unbridled activation of cytotoxic T lymphocytes, natural killer (NK) cells, and macrophages resulting in hypercytokinemia, extreme inflammation and immune-mediated injury of multiple organ systems. It is seen in both children and adults and is recognized as primary (driven by underlying genetic mutations that abolish critical proteins required for normal function of cytotoxic T cells and NK Cells) or secondary (resulting from a malignant, infectious, or autoimmune stimulus without an identifiable underlying genetic trigger). In primary HLH, hematopoietic stem cell transplant (HSCT) is required for cure. Without any treatment, survival in primary HLH is approximately 2 months.

#### **Gamifant (emapalumab-lzsg) – Medical Benefit**

#### Policy Criteria:

Gamifant is a fully human monoclonal antibody against interferon gamma (IFN- $\gamma$ ) and is considered medically necessary when all the following requirements are met (a – g):

- a. Prescribed by a physician who specializes in the treatment of HLH (such as a hematologist, oncologist, immunologist or transplant specialist) AND
- b. The patient has a diagnosis of Primary HLH confirmed by at least one of the following (either i., ii., or iii)
  - i. Genetic testing confirming biallelic pathogenic variants (e.g., PRF1, UNC13D/MUNC13-4, STX11 or STXBP2) OR
  - ii. Positive family history (affected siblings or parental consanguinity) consistent with primary HLH in a symptomatic individual OR
  - iii. Meet at least FIVE out of the following diagnostic criteria prior to treatment:
    - a) Low or absent NK-cell activity (according to local laboratory reference)
    - b) Fever  $\geq 38.5^{\circ}\text{C}$  (or  $101.3^{\circ}\text{F}$ )
    - c) Splenomegaly
    - d) Elevated ferritin  $\geq 500$  micrograms/L
    - e) Elevated CD25 (i.e. soluble IL-2 receptor)  $\geq 2,400$  U/mL
    - f) Hypertriglyceridemia (fasting triglycerides  $\geq 265$  mg/dL (3 mmol/L) and/or hypofibrinogenemia (fibrinogen  $\leq 1.5$ g/L)
    - g) Hemophagocytosis in bone marrow or spleen or lymph nodes
    - h) Cytopenias affecting at least 2 of 3 lineages in the peripheral blood:
      - Hemoglobin  $< 9$  g/dL (or  $< 10$ g/dL in infants  $< 4$  weeks of age)
      - Platelets  $< 100 \times 10^9$ /L
      - Neutrophils  $< 1 \times 10^9$ /L, AND
- c. Evidence of active disease that is refractory, recurrent or progressive despite at least ONE conventional HLH therapy OR severe intolerance to at least ONE conventional therapy. Examples of conventional HLH treatments include etoposide and dexamethasone,

## Pharmacy Management Drug Policy

### Inborn Errors of Metabolic Diseases

cyclosporine A, anti-thymocyte globulin and intrathecal methotrexate following a standard of care treatment protocol AND

- d. Administer dexamethasone concomitantly with Gamifant, AND
- e. Administer Gamifant until hematopoietic stem cell transplantation (HSCT) is performed or unacceptable toxicity. Discontinue Gamifant when patient no longer requires therapy for the treatment of HLH.
- f. Prior authorization for Gamifant will apply regardless of the site of administration (applies to both the inpatient and outpatient setting). Gamifant must be administered by a healthcare professional and is covered under the medical benefit AND
- g. Gamifant is dosed based on body weight. Therefore, current body weight and requested dose regimen must be submitted for initial review and each recertification request AND

#### Approval Information:

- Initial approval will be for 2-month duration.
- Continuation of therapy at 2-month intervals will require documentation of therapeutic benefit:
  - c. Complete response defined as normalization of all HLH abnormalities (i.e., no fever, no splenomegaly, neutrophils  $> 1 \times 10^9/L$ , platelets  $> 100 \times 10^9/L$ , ferritin  $< 2,000 \text{ ug/L}$ , fibrinogen  $> 1.50 \text{ g/L}$ , D-dimer  $< 500 \text{ ug/L}$ , normal CNS symptoms, no worsening of sCD25  $> 2$ -fold baseline);  
**OR**
  - d. Partial response defined as normalization of  $\geq 3$  HLH abnormalities; **OR**
  - e. HLH improvement defined as  $\geq 3$  HLH abnormalities improved by at least 50% from baseline

#### Additional Drug Information:

- Recommended starting dose is 1mg/kg twice per week via IV infusion. Dose may be increased based on clinical and laboratory findings up to a maximum dose of 10mg/kg

**Adenosine Deaminase Severe Combined Immune Deficiency (ADA-SCID)** is an ultra-rare, autosomal recessive genetic disorder of purine metabolism affecting lymphocyte development, viability and function. ADA-SCID is typically diagnosed before 1 year of age; affected infants have marked depletion of B, T, and natural killer (NK) lymphocytes. Manifestations include persistent diarrhea, extensive dermatitis, recurrent pneumonia, and other life-threatening illnesses caused by opportunistic infections. Hematopoietic stem cell therapy (HSCT) or gene therapy are the only curative treatments. Enzyme replacement therapy (with Revcovi or Adagen) is recommended as a bridge to curative therapy or as maintenance therapy in patients who have failed or are unsuitable for more definitive treatments. Without any treatment, patients with ADA-SCID rarely survive beyond 1 to 2 years of age.

#### **Revcovi (elapegademase-lvlr) – Pharmacy benefit**

##### Policy Criteria:

Revcovi is a recombinant adenosine deaminase indicated for treatment of ADA-SCID in pediatric and adult patients and is considered medically necessary when ALL the following requirements have been met (a - e):

- a. Prescribed by or in consultation with an immunologist, hematologist/oncologist or a physician that specializes in the treatment of ADA- SCID AND
- b. The patient has a diagnosis of ADA-SCID confirmed by one of the following (i. or ii)
  - i. Absent or very low ( $< 1\%$  of normal) adenosine deaminase (ADA) catalytic activity in plasma, urine or dried blood spots prior to the initiation of enzyme replacement therapy **OR**
  - ii. Molecular genetic testing confirming bi-allelic mutations in the ADA gene, AND
- c. Must have elevated deoxyadenosine triphosphate (dATP) levels or total deoxyadenosine (dAdo) nucleotides in erythrocytes (red blood cells) compared to a laboratory standard, AND
- d. Patient is not a suitable candidate for hematopoietic cell transplantation (HCT) at the time of the request **OR** patient has failed HCT, AND

## Pharmacy Management Drug Policy

### Inborn Errors of Metabolic Diseases

- e. Must not have severe thrombocytopenia (considered to be a platelet count of < 50,000 cells/microliter)
- f. Revcovi is dosed based on patient weight; therefore, current body weight and requested dose regimen must be submitted for initial review and each recertification request.
- g. Revcovi may be self-administered after appropriate training from a healthcare professional and therefore is covered under the pharmacy benefit.

#### Approval Information:

- Initial approval will be for one year.
- Recertification every two years thereafter will require documentation of a positive response to treatment such as one or more of the following:
  - Improvement in immune status (total lymphocyte and B, T, and natural killer (NK) lymphocyte counts, quantitative immunoglobulin (Ig) concentration [IgG, IgA, IgM])
  - Improvement in clinical status (infection rate, incidence and duration of hospitalization, and performance status)
  - Normalization of plasma ADA activity, erythrocyte dATP or total dAdo nucleotide levels compared to a laboratory standard

#### Additional Drug Information:

- The starting dose of Revcovi depends on whether the patient was previously using Adagen. Please refer to the FDA approved prescribing literature for additional dosing and monitoring guidance.
  - Adagen-naïve patients: the starting weekly dose of Revcovi is 0.4 mg/kg IM based on ideal body weight, divided into two doses (0.2 mg/kg twice weekly), for a minimum of 12 to 24 weeks until immune reconstitution is achieved.
  - Transitioning from Adagen to Revcovi:
    - (1) Previous Adagen weekly dose unknown or dose  $\leq$  30 U/kg: Revcovi dose minimum of 0.2 mg/kg intramuscularly once weekly
    - (2) Previous Adagen weekly dose > 30 U/kg: Calculate Revcovi dose based on the following formula: Revcovi dose (mg/kg) = Adagen dose (U/kg) / 150

#### **Adagen (pegademase bovine) – Pharmacy benefit**

##### Policy Criteria:

Adagen is a modified adenosine deaminase enzyme indicated for treatment of ADA-SCID in pediatric and adult patients who are not suitable candidates for, or who have failed, bone marrow transplantation and is considered medically necessary when all the following requirements have been met (a - f):

- a. Please note: Coverage of Adagen will ONLY be considered on a case by case basis, if product is available, as Adagen is being discontinued due to the permanent shortage of the active ingredient.
- b. Prescribed by or in consultation with an immunologist, hematologist/oncologist or a physician that specializes in the treatment of ADA- SCID AND
- c. The patient has a diagnosis of ADA-SCID confirmed by one of the following (i. or ii)
  - i. Absent or very low (< 1% of normal) adenosine deaminase (ADA) catalytic activity in plasma, urine or dried blood spots prior to the initiation of enzyme replacement therapy OR
  - ii. Molecular genetic testing confirming bi-allelic mutations in the ADA gene, AND
- d. Must have elevated deoxyadenosine triphosphate (dATP) levels or total deoxyadenosine (dAdo) nucleotides in erythrocytes (red blood cells) compared to a laboratory standard, AND
- e. Patient is not a suitable candidate for hematopoietic cell transplantation (HCT) at the time of the request OR patient has failed HCT, AND
- f. Adagen is dosed based on patient weight; therefore, current body weight and requested dose regimen must be submitted for initial review and each recertification request

## Pharmacy Management Drug Policy

### Inborn Errors of Metabolic Diseases

#### Approval Information:

- Initial approval will be for one year.
- Recertification every two years thereafter will require documentation of a positive response to treatment such as one or more of the following:
  - Improvement in immune status (total lymphocyte and B, T, and natural killer (NK) lymphocyte counts, quantitative immunoglobulin (Ig) concentration [IgG, IgA, IgM])
  - Improvement in clinical status (infection rate, incidence and duration of hospitalization, and performance status)
  - Normalization of plasma ADA activity, erythrocyte dATP or total dAdo nucleotide levels compared to a laboratory standard

#### Additional Drug Information:

- Adagen may be self-administered after appropriate training from a healthcare professional and therefore is covered under the pharmacy benefit.
- A maximum single dose of 30 U/kg should not be exceeded per FDA approved labeling
- Adagen is administered every 7 days as an intramuscular injection. The recommended dosing schedule is 10 U/kg for the first dose, 15 U/kg for the second dose, and 20 U/kg for the third dose. The usual maintenance dose is 20 U/kg per week. Further increases of 5 U/kg/week may be necessary
- There is no evidence to support the safety and efficacy of Adagen as preparatory or support therapy for bone marrow transplantation

#### **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.

<b>HCPCS:</b>	J1931	Aldurazyme
	J0567	Brineura
	J1786	Cerezyme
	J0584	Crysvita
	J3060	Elelyso
	J1743	Elaprase
	J0180	Fabrazyme
	J9210	Gamifant
	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

# Pharmacy Management Drug Policy

## Inborn Errors of Metabolic Diseases

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

<u>Line of Business</u>	<u>Rx Initial approval</u>	<u>Rx Continued approval</u>	<u>Medical Initial approval</u>	<u>Medical Recert</u>
<b>Medicaid Managed Care (MMC) / Child Health Plus (CHP)</b>	1 year (or as stated within individual drug policy)	2 years	6 months	12 months
<b>Commercial / Exchange</b>	1 year (or as stated within individual drug policy)	2 years	Outpatient Hospital – 6 months	Outpatient Hospital – 6 months
			Home Care or Office Based – 2 years	Home Care or Office Based – 2 years
<b>Medicare</b>	Defined in Medicare Drug Policy	Defined in Medicare Drug Policy	Outpatient Hospital – 6 months	Outpatient Hospital – 6 months
			Home Care or Office Based – 2 years	Home Care or Office Based – 2 years

### Policy Guidelines:

1. Prior authorization is contract dependent.
2. 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.
3. 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.
4. 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.
5. 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

# Pharmacy Management Drug Policy

## Inborn Errors of Metabolic Diseases

- 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 rationale 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.

### UPDATES:

Date:	Revision:
11/2019	Revised
10/2019	Revised
9/2019	Revised
7/2019	Revised
3/19	Revised
2/19	Committee Approval
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
2/16	Revised
1/16	Revised
5/15	Revised
9/14	Revised
3/14	Revised
4/13	Revised
7/12	Revised
4/11	Revised
7/10	Revised
4/10	Revised
10/09	Reviewed
9/08	Revised
3/07	Created

### REFERENCES:

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:

#### **Gaucher Disease**

1. Berge KMD. Gaucher's Disease. [www.mayoclinic.com/health/gauchers-disease/AN00840](http://www.mayoclinic.com/health/gauchers-disease/AN00840). Accessed September 11, 2006.
2. McGovern M. Gaucher Disease. *eMedicine*; 2003.
3. Weinreb N. Imiglucerase and its use for the treatment of Gaucher's disease. *Expert Opinion in Pharmacotherapy*. 2008 Aug;9(11):1987-2000.
4. Vellodi A, Bembi B, de Villemeur TB, et al. Management of neuronopathic Gaucher disease: a European consensus. *J Inher Metab Dis* 2001; 24:319

# Pharmacy Management Drug Policy

## Inborn Errors of Metabolic Diseases

5. Vellodi A, Tylki-Szymanska A, Davies EH, et al. Management of neuronopathic Gaucher disease: Revised recommendations. *J Inherit Metab Dis* 2009; 32:660.
6. Martins A, Valadares E, Porta G, et al. Recommendations on Diagnosis, Treatment and Monitoring for Gaucher disease. *The Journal of Pediatrics*. Oct 2009;155(4): S10-S18.

### Fabry disease

1. Eng Christine GN, Wilcox W, Germain D, Lee P, Waldek S, Caplan L, Linthorst G, Desnick R. Safety and Efficacy of Recombinant Human (alpha)-Galactosidase A Replacement Therapy in Fabry's Disease. *The New England Journal of Medicine*. July 5 2001 2001;345(1):9-16.
2. Wasserstein M. Fabry Disease. *eMedicine*. 2004(Topic2888).
3. Maurer M, Kopp JB, Schiffmann R. Fabry disease: Clinical features and diagnosis. UpToDate <https://www.uptodate.com/contents/fabry-disease-clinical-features-and-diagnosis>
4. Germain DP, Hughes DA, Nicholls K, et al. Treatment of Fabry's Disease with the Pharmacologic Chaperone Migalastat. *N Engl J Med* 2016; 375:545-555.
5. Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document. *Orphanet Journal of Rare Diseases*. 2015;10:36 <https://doi.org/10.1186/s13023-015-0253-6>
6. Ortiz A, Germain DP, Desnick RJ, et al. Fabry disease revisited: Management and treatment recommendations for adult patients. *Molecular Genetics and Metabolism* 2018;123:416-427
7. Hopkin R, Jeffries L, Laney D, et.al. The Management and treatment of children with Fabry disease: A United States-based perspective. *Molecular Genetics and Metabolism*. 2016; 117 (2): 104-113.
8. Eng C, Germain D, Banikazemi M. Fabry disease: Guidelines for the evaluation and management of multi-organ system involvement. *Genetics in Medicine*. 2006; 8 (9).

### Tyrosinemia Type 1

1. Roth K. Tyrosinemia. *eMedicine*. 2006(Topic2339).

### Congenital Sucrase-Isomaltase deficiency

1. QOL Medical. How to diagnose CSID. [http://www.sucraid.net/diagnose\\_csid.html](http://www.sucraid.net/diagnose_csid.html). Accessed 8/16/17.

### Pompe Disease

1. Bembi B, Cerini E, Danesino C, et al. Diagnosis of glycogenosis type II. *Neurology*. Dec 2008;71(23): S4-S11.

### Mucopolysaccharidosis

1. Panel VPBMSHCGatMA. Laronidase (Aldurazyme): National PBM Drug Monographs; 2004
2. Fenton C. Mucopolysaccharidosis Type II. *eMedicine*. 2006(Topic1029).
3. Ibrahim J. Glycogen-Storage Disease Type II. *eMedicine*. 2006(Topic1866).
4. McGovern M. Mucopolysaccharidosis Type VI. *eMedicine*. 2005(Topic1373).
5. Medicine EUSo. Emory Genetics Lab Test Database: Department of Human Genetics 2006.
6. Nash D. Mucopolysaccharidosis Type IH. *eMedicine*. 2003(Topic1031).

### N-acetylglutamate Synthase deficiency and Urea Cycle Disorders

1. Mew NA, Simpson KL, Gropman AL, et al. Urea Cycle Disorders Overview. *Genereviews* (internet). Accessed 11/1/2018

### Bile Acid Synthesis Disorders

1. Heubi JE, Setchell KD, Bove KE. Inborn Errors of Bile Acid Metabolism. *Seminars in Liver Disease* 2007; 27(2): 282-294.

### Lysosomal Acid Lipase deficiency

1. Reiner Z, Guardamagna O, Nair D, et al. Lysosomal acid lipase deficiency--an under-recognized cause of dyslipidaemia and liver dysfunction. *Atherosclerosis*. Jul 2014;235(1):21-30. PMID 24792990
2. Bernstein DL, Hulkova H, Bialer MG, Desnick RJ. Cholesteryl ester storage disease: review of the findings in 135 reported patients with an underdiagnosed disease. *J Hepatol*. Jun 2013;58(6):1230-1243.

### Hypophosphatasia

1. Asfotase Alfa. BCBSA Specialty Pharmacy Report. BlueCross BlueShield Association. <http://bluewebportal.bcbs.com/documents>. Accessed 8/16/17.
2. Alkaline Phosphatase Isoenzymes, Serum or Plasma, ARUP Laboratories. <http://ltd.aruplab.com/tests/pup/0021020>. Accessed 8/16/17.

# Pharmacy Management Drug Policy

## Inborn Errors of Metabolic Diseases

### Hereditary Orotic Aciduria

1. Balasubramaniam S, Duley JA, Christodoulou J. Inborn errors of pyrimidine metabolism: clinical update and therapy. *J Inher Metab Dis* 2014; 37:687-98
- FDA. [Press Release]. FDA approves new orphan drug to treat rare autosomal recessive disorder. Available at: <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm457867.htm>. Updated September 4, 2015.

### Ceroid Lipofuscinosis Type 2 (CLN2) / tripeptidyl peptidase 1 (TPP1) deficiency

1. Steinfeld, R., Heim, P., von Gregory, H., Meyer, K., Ullrich, K., Goebel, H. H. and Kohlschütter, A. (2002), Late infantile neuronal ceroid lipofuscinosis: Quantitative description of the clinical course in patients with *CLN2* mutations. *Am. J. Med. Genet.*, 112: 347–354. doi:10.1002/ajmg.10660
2. Fietz M, ALSayed M, Burke D, et.al. Diagnosis of neuronal ceroid lipofuscinosis type 2 (CLN2 disease); Expert recommendations for early detection and laboratory diagnosis. *Molecular Genetics and Metabolism*. 2016. 119(1),160-167.  
<http://www.cln2connection.com/overview/natural-history/>. Accessed June 2017

### X-linked hypophosphatemia

1. Ruppe MD. X-linked hypophosphatemia. GeneReviews®. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK83985/>. Updated April 13, 2017, Accessed 05/25/2018
2. Scheinman SJ, Drezner MK. Hereditary hypophosphatemia rickets and tumor-induced osteomalacia. UpToDate, Inc. Available at: [www.uptodate.com](http://www.uptodate.com). Updated September 26, 2017
3. Bacon S, Crowley R. Developments in rare bone diseases and mineral disorders. *Ther Adv Chronic Dis*. 2018;9(1):51-60.
4. Lambert AS, Linglard A. Hypocalcaemic and hypophosphatemic rickets. *Best Practice & Research: Clinical Endocrinology & Metabolism*. Aug 2018; 32(4): 455-476
5. Fibroblast Growth Factor 23 in Oncogenic Osteomalacia and X-Linked Hypophosphatemia. Jonsson KB, Zahradnik R et. al. *N Engl J Med* 2003; 348:1656-1663
6. Clinical usefulness of measurement of fibroblast growth factor 23 (FGF23) in hypophosphatemic patients. *Bone* 2008. 42(6):1235-1239

### Phenylketonuria

1. Palynziq™ injection for subcutaneous use [prescribing information]. Novato, CA: BioMarin Pharmaceutical Inc.; June 2018.
2. Harding CO, Amato RS, Stuy M, et al. Pegvaliase for the treatment of phenylketonuria: a pivotal, double-blind randomized discontinuation Phase 3 clinical trial. *Mol Genet Metab*. 2018;124(1):20-26.
3. Thomas J, Levy H, Amato S, et al. Pegvaliase for the treatment of phenylketonuria: results of a long-term phase 3 clinical trial program (PRISM). *Mol Genet Metab*. 2018;124(1):27-38.

### Transthyretin-mediated amyloidosis (hATTR)

1. Ando Y, Coelho T, et.al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet J Rare dis*. 2013; 8: 31
2. Gertz M, Benson M, Dyck P. Diagnosis, Prognosis, and Therapy of Transthyretin Amyloidosis. *Journal of the American College of Cardiology*. 2015: 66 (21), 2451 – 2466
3. Siddiqui O, Ruberg F. Cardiac Amyloidosis: An update on pathophysiology, diagnosis, and treatment. *Trends in Cardiovascular Medicine*. 2018; 28(1): 10-21.
4. Maurer MS, Elliott P, Merlini G, et al. Design and rationale of the Phase 3 ATTR-ACT clinical trial (tafamidis in transthyretin cardiomyopathy clinical trial). *Circ Heart Fail*. 2017;10(6).

### Hemophagocytic lymphohistiocytosis (HLH):

1. Henter J, Horne A, Arico M, et.al. HLH-2004: Diagnostic and Therapeutic Guidelines for Hemophagocytic Lymphohistiocytosis. *Pediatr Blood Cancer* 2007;48:124-131
2. Al-Samkari H, Berliner N. Hemophagocytic Lymphohistiocytosis. *Annu. Rev. Path. Mech. Dis*. 2018;13:27-49.
3. McClain K. Treatment and Prognosis of hemophagocytic lymphohistiocytosis. UpToDate. Last updated 12/14/2018. Accessed 1/21/2019.

### Adenosine Deaminase Severe Combined Immune Deficiency (ADA-SCID)

1. Kohn DB, Hershfield MS, Puck JM, et al. Consensus approach for the management of severe combined immune deficiency caused by adenosine deaminase deficiency. *J Allergy Clin Immunol*. 2018 September 5. [Epub ahead of print].



**Pharmacy Management Drug Policy**  
Inborn Errors of Metabolic Diseases