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Subject: Enzyme Replacement Therapy for Pompe Disease

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DESCRIPTION:

Pompe disease, or glycogen storage disease type II (GSD II), is an autosomal-recessive lysosomal storage disorder that causes a deficiency of the enzyme acid alpha-glucosidase (GAA). When GAA is not present in adequate amounts, lysosomal glycogen accumulates in tissues throughout the body, most often in the skeletal, cardiac, and smooth muscles. The severity of the disease varies based on the age of onset, organ involvement, rate of progression, and severity/degree of muscle involvement. Pompe disease is diagnosed by GAA enzyme activity in the blood and/or other tissue, and genetic sequencing. The presence of two pathogenic variants in the GAA gene is sufficient to diagnose Pompe disease; however, some patients may only have one pathogenic variant.

Pompe disease is treated with enzyme replacement therapy (ERT) – currently there are three FDA approved products available: alglucosidase alfa (Lumizyme), avalglucosidase alfa-ngpt (Nexviazyme), and cipaglucosidase alfa-atga (Pombiliti) in combination with miglustat (Opfolda). Algucosidase is approved for treatment of both infantile-onset Pompe disease and late-onset Pompe disease. Avalglucosidase and cipaglucosidase alfa-atga (in combination with miglustat) areapproved for treatment of late-onset Pompe disease only.

Alglucosidase alfa (Lumizyme)

The safety and efficacy of alglucosidase alfa were assessed in an international, multicenter, open-label, clinical trial of 18 infantile-onset Pompe disease patients. Patients were randomized 1:1 to receive either 20 mg/kg or 40 mg/kg alglucosidase alfa every two weeks, with length of treatment ranging from 52 to 106 weeks. Enrollment was restricted to patients 7 months of age or younger at first infusion with clinical signs of Pompe disease and cardiac hypertrophy, and who did not require ventilatory support at

study entry. Fourteen patients were cross reactive immunologic material (CRIM) positive and 4 patients were CRIM negative.

Efficacy was assessed by comparing the proportions of alglucosidase alfa-treated patients who died or needed invasive ventilator support at 18 months of age with the mortality experience of a historical cohort of untreated infantile-onset Pompe disease patients with similar age and disease severity. In the historical cohort, 61 untreated patients with infantile-onset Pompe disease diagnosed by age 6 months, born between 1982 and 2002, were identified by a retrospective review of medical charts. By 18 months of age, 15 of 18 (83%) alglucosidase alfa-treated patients were alive without invasive ventilatory support and 3 (17%) required invasive ventilator support, whereas only one of the 61 (2%) historical control patients was alive. No differences in outcome were observed between patients who received 20 mg/kg versus 40 mg/kg.

Other outcome measures in this study included unblinded assessments of motor function by the Alberta Infant Motor Scale (AIMS), a measure of infant motor performance that assesses motor maturation of the infant through age 18 months. Although gains in motor function were noted in 13 patients, the motor function was substantially delayed compared to normal infants of comparable age in the majority of patients. Two of 9 patients who had initially demonstrated gains in motor function after 12 months of alglucosidase alfa treatment regressed despite continued treatment.

Changes from baseline to Month 12 in left ventricular mass index (LVMI), a measure of pharmacodynamic effect, were evaluated by echocardiography. Fifteen patients who underwent both baseline and Month 12 echocardiograms demonstrated decreases from baseline in LVMI (mean decrease 118 g/m2, range 45 to 193 g/m2). However, the magnitude of the decrease in LVMI did not correlate with the clinical outcome measure of ventilator-free survival.

The safety and efficacy of alglucosidase alfa were assessed in 90 patients with late-onset Pompe disease, aged 10 to 70 years, in a randomized, double-blind, placebo-controlled trial. All patients were naive to enzyme replacement therapy. Patients were allocated in a 2:1 ratio and received 20 mg/kg alglucosidase alfa (n=60) or placebo (n=30) every other week for 78 weeks (18 months). At baseline, all patients were ambulatory (some required assistive walking devices), did not require invasive ventilator support or non-invasive ventilation while awake and sitting upright, and had a forced vital capacity (FVC) between 30 and 79% of predicted in the sitting position. Patients who could not walk 40 meters in 6 minutes or were unable to perform appropriate pulmonary and muscle function testing were excluded from the study.

A total of 81 of 90 patients completed the trial. Of the 9 patients who discontinued, 5 were in the alglucosidase alfa group and 4 were in the placebo group. Three patients discontinued the study due to an adverse event; two patients were in the alglucosidase alfa treatment group and one patient was in placebo group.

At study entry, the mean % predicted FVC in the sitting position among all patients was about 55%. After 78 weeks, the mean % predicted FVC increased to 56.2% for alglucosidase alfa-treated patients and decreased to 52.8% for placebo-treated patients indicating an alglucosidase alfa treatment effect of 3.4% (95% confidence interval: [1.3% to 5.5%]; p=0.004). Stabilization of % predicted FVC in the alglucosidase alfa-treated patients was observed. t study entry, the mean 6 minute walk test (6MWT) among all patients was about 330 meters. After 78 weeks, the mean 6MWT increased by 25 meters for

alglucosidase alfa-treated patients and decreased by 3 meters for placebo-treated patients indicating an alglucosidase alfa treatment effect of 28 meters (95% confidence interval: [-1 to 52 meters]; p=0.06).

Avalglucosidase alfa-ngpt (Nexviazyme)

The safety and efficacy of avalglucosidase were compared to alglucosidase alfa in 100 treatment naïve patients with late-onset Pompe disease in a phase 3, randomized, double-blind noninferiority study. Patients were randomized in a 1:1 ratio based on baseline forced vital capacity (FVC), gender, age, and country to receive 20 mg/kg of avalglucosidase or alglucosidase alfa administered intravenously once every two weeks for 49 weeks. The primary endpoint was the change in FVC (% predicted) in the upright position from baseline to week 49. Change in 6MWT was a secondary endpoint.

Patients treated with avalglucosidase alfa-ngpt had FVC (% predicted) increase of 2.9% compared with 0.5% in those treated with alglucosidase alfa. The estimated difference in FVC between the groups was 2.4 (95% CI, -0.1 to 5) from baseline to week 49. Avalglucosidase alfa-ngpt significantly increased the distance walked in a 6MWT at week 49 by a mean of 32.2 meters compared with 2.2 meters in patients who received alglucosidase alfa. The estimated difference in distance walked between the groups was 30 meters (95% CI, 1.3 to 58.7) from baseline to week 49.

Cipaglucosidase alfa-atga (Pombiliti) in combination with miglustat (Opfolda)

The safety and efficacy of cipaglucosidase alfa-atga were evaluated in adult patients (n=123) with late-onset Pompe disease in the PROPEL study. Patients were randomized 2:1 to receive either cipaglucosidase alfa 20 mg/kg IV every 2 weeks plus miglustat 195 mg for patients weighing 40 to less than 50 kg or 260 mg for patients weighing 50 kg or greater (n=85), or alglucosidase alfa 20 mg/kg IV every 2 weeks plus placebo (n=38); miglustat and placebo were administered 1 hour prior to the IV infusions.

After 52 weeks, the mean change in 6-minute walk distance (6MWD) in patients receiving cipaglucosidase alfa plus miglustat was numerically but not significantly greater than that of patients receiving alglucosidase alfa plus placebo (20.8 m vs 7.2 m; between-group difference, 13.6 m [95% CI, -2.8 to 29.9]). The change from baseline in percent predicted sitting FVC was significantly lower at week 52 in the cipaglucosidase alfa plus miglustat group compared with alglucosidase alfa (mean change, -0.9% vs -4%; between-group difference, 3% [95% CI, 0.7 to 5.3]); sitting FVC (% predicted) stabilized in enzyme-replacement therapy (ERT)-experienced patients treated with cipaglucosidase alfa compared with worsening in ERT-experienced patients treated with alglucosidase alfa. In ERT-naïve patients, alglucosidase plus placebo was associated with a numerical but not significant advantage over cipaglucosidase alfa plus miglustat in the mean change in 6MWD and sitting FVC. In the overall population, ERT-experienced, and ERT-naïve patients, creatine kinase and urinary glucose tetrasaccharide (Hex4) levels were significantly reduced at week 52 in the cipaglucosidase alfa plus miglustat group compared with alglucosidase alfa plus placebo.

Serious treatment-emergent adverse events occurred in 9% of patients receiving cipaglucosidase alfa plus miglustat compared with 3% receiving alglucosidase alfa plus placebo; only 1 event in the cipaglucosidase alfa group was attributed to study treatment. The most frequently reported adverse events included falls (29% vs 39%), headache (24% vs 24%), nasopharyngitis (22% vs 8%), myalgia (16% vs 13%), arthralgia (15% vs 13%), and urinary tract infection (14% vs 5%). Infusion-associated reactions

occurred in 25% and 26% of patients, and 3 patients in the cipaglucosidase alfa group and 1 patient in the alglucosidase alfa group withdrew from the study due to adverse events.

POSITION STATEMENT:

Initiation of enzyme replacement therapy for Pompe disease **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member is diagnosed with infantile-onset Pompe disease (alglucosidase alfa [Lumizyme]) or late-onset Pompe disease (alglucosidase alfa [Lumizyme], avalglucosidase alfa-ngpt [Nexviazyme], (cipaglucosidase alfa-atga [Pombiliti])
2. Member's diagnosis is confirmed by one of the following:
    a. Infantile-Onset Pompe Disease – alglucosidase alfa [Lumizyme) **ONLY**
        i. Acid alpha-glucosidase (GAA) enzyme activity level less than or equal to 1% of normal – laboratory documentation must be provided
        ii. Two mutations in the GAA gene – laboratory documentation must be provided
    b. Late-Onset Pompe Disease
        i. Acid alpha-glucosidase (GAA) enzyme activity level less than or equal to 40% of normal – laboratory documentation must be provided
        ii. Two mutations in the GAA gene – laboratory documentation must be provided
3. Member disease is symptomatic (e.g., cardiac hypertrophy, respiratory distress, skeletal muscle weakness, etc.) – documentation from the medical record must be provided
4. Treatment is limited to a single enzyme replacement product

    NOTE: If switching enzyme replacement therapy, member's medical record will be reviewed and any current authorizations for algucosidase alfa, avalglucosidase alfa-ngpt, or cipaglucosidase alfa-atga will be terminated upon approval of the requested agent

5. Cipaglucosidase alfa-atga (Pombiliti) **ONLY**:
    a. Member is currently treated with enzyme replacement therapy **AND** is not improving – documentation from the medical record must be provided
    b. Member weighs at least 40 kg
    c. Use will be in combination with miglustat (Opfolda)
6. Dose does not exceed:
    a. alglucosidase (Lumizyme): 20 mg/kg every two weeks
    b. avalglucosidase-ngpt (Nexviazyme):
        i. Weight ≥30 kg: 20 mg/kg every two weeks
        ii. Weight <30 kg: 40 mg/kg every two weeks
    c. cipaglucosidase alfa-atga (Pombiliti):
        i. Weight ≥ 40 kg: 20 mg/kg every two weeks

Approval duration: 1 year

Continuation of enzyme replacement therapy for Pompe disease **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Authorization/reauthorization has been previously approved by Florida Blue in the past two years for treatment of infantile-onset Pompe disease (alglucosidase [Lumizyme]) or late-onset Pompe disease (alglucosidase alfa [Lumizyme], avalglucosidase alfa-ngpt [Nexviazyme], (cipaglucosidase alfa-atga [Pombiliti]) (if another health plan, documentation of a health plan-paid claim for requested product during the 90 days immediately before the request must be submitted), **OR** the member has previously met all indication-specific criteria
2. Member is receiving a beneficial response (such as, but not limited to, improved motor function, endurance, % predicted FVC) to treatment with enzyme replacement therapy – documentation from the medical record must be provided
3. Treatment is limited to a single enzyme replacement product

   NOTE: If switching enzyme replacement therapy, member's medical record will be reviewed and any current authorizations for algucosidase alfa or avalglucosidase alfa-ngpt will be terminated upon approval of the requested agent
4. Cipaglucosidase alfa-atga (Pombiliti) **ONLY**:
   a. Member weighs at least 40 kg
   b. Use will be in combination with miglustat (Opfolda)
5. Dose does not exceed:
   a. alglucosidase (Lumizyme): 20 mg/kg every two weeks
   b. avalglucosidase-ngpt (Nexviazyme):
      i. Weight ≥30 kg: 20 mg/kg every two weeks
      ii. Weight <30 kg: 40 mg/kg every two weeks
   c. cipaglucosidase alfa-atga (Pombiliti):
      i. Weight ≥ 40 kg: 20 mg/kg every two weeks

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Lumizyme (alglucosidase alfa): 20 mg per kg body weight administered every two weeks as an intravenous infusion

- Nexviazyme (avalglucosidase alfa-ngpt):
    - ≥30 kg, the recommended dosage is 20 mg/kg (of actual body weight) every two weeks
    - <30 kg, the recommended dosage is 40 mg/kg (of actual body weight) every two weeks
- Pombiliti (cipaglucosidase alfa-atga):
    - ≥40 kg: 20 mg/kg (of actual body weight) every two weeks
    - Start in combination with Opfolda (miglustat) two weeks after the last ERT dose
    - Initiate infusion approximately 1 hour after oral administration of Opfolda

Dose Adjustments

- None

Drug Availability

- Lumizyme (alglucosidase alfa): 50 mg of alglucosidase alfa as lyophilized powder in a single-dose vial for reconstitution
- Nexviazyme (avalglucosidase alfa-ngpt): 100 mg of avalglucosidase alfa-ngpt as a lyophilized powder in a single-dose vial for reconstitution
- Pombiliti (cipaglucosidase alfa-atga): 105 mg of cipaglucosidase alfa-atga as a lyophilized powder in a single-dose vial for reconstitution

PRECAUTIONS:

Boxed Warning

- Lumizyme (alglucosidase alfa):
    - Life-threatening anaphylactic reactions and severe hypersensitivity reactions have occurred in some patients during and after alglucosidase alfa infusions. Immune-mediated reactions presenting as proteinuria, nephrotic syndrome, and necrotizing skin lesions have occurred in some patients following alglucosidase alfa treatment. Closely observe patients during and after alglucosidase alfa administration and be prepared to manage anaphylaxis and hypersensitivity reactions. Inform patients of the signs and symptoms of anaphylaxis, hypersensitivity reactions, and immune-mediated reactions and have them seek immediate medical care should signs and symptoms occur.
    - Infantile-onset Pompe disease patients with compromised cardiac or respiratory function may be at risk of serious acute exacerbation of their cardiac or respiratory compromise due to fluid overload and require additional monitoring.
- Nexviazyme (avalglucosidase alfa-ngpt):
    - Hypersensitivity Reactions Including Anaphylaxis: Patients treated with NEXVIAZYME have experienced life-threatening hypersensitivity reactions, including anaphylaxis. Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available.

- Infusion-Associated Reactions (IARs): Patients treated with NEXVIAZYME have experienced severe IARs. If severe IARs occur, consider immediate discontinuation of NEXVIAZYME, initiation of appropriate medical treatment, and the benefits and risks of readministering NEXVIAZYME following severe IARs. Patients with an acute underlying illness at the time of NEXVIAZYME infusion may be at greater risk for IARs. Patients with advanced Pompe disease may have compromised cardiac and respiratory function, which may predispose them to a higher risk of severe complications from IARs.
- Risk of Acute Cardiorespiratory Failure in Susceptible Patients:
- Patients susceptible to fluid volume overload, or those with acute underlying respiratory illness or compromised cardiac or respiratory function for whom fluid restriction is indicated may be at risk of serious exacerbation of their cardiac or respiratory status during NEXVIAZYME infusion. More frequent monitoring of vitals should be performed during NEXVIAZYME infusion in such patients.

- Pombiliti (cipaglucosidase alfa-atga):
  - Hypersensitivity Reactions Including Anaphylaxis: Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available. If a severe hypersensitivity reaction occurs, POMBILITI should be discontinued immediately, and appropriate medical treatment should be initiated.
  - Infusion-Associated Reactions (IARs): If severe IARs occur, immediately discontinue POMBILITI and initiate appropriate medical treatment.
  - Risk of Acute Cardiorespiratory Failure in Susceptible Patients: Patients susceptible to fluid volume overload, or those with acute underlying respiratory illness or compromised cardiac or respiratory function, may be at risk of serious exacerbation of their cardiac or respiratory status during POMBILITI infusion.

Contraindications

- Lumizyme (alglucosidase alfa): None
- Nexviazyme (avalglucosidase alfa-ngpt): None
- Pombiliti (cipaglucosidase alfa-atga): Pregnancy

Precautions/Warnings

- Lumizyme (alglucosidase alfa):
  - Anaphylaxis and Hypersensitivity Reactions: Life-threatening anaphylaxis and hypersensitivity reactions have been observed in some patients during and after treatment with alglucosidase alfa. Ensure that appropriate medical support measures, including cardiopulmonary resuscitation equipment, are readily available. If anaphylaxis or severe hypersensitivity reactions occur, immediately discontinue infusion and initiate appropriate medical treatment.
  - Immune-Mediated Reactions: Monitor patients for the development of systemic immune-mediated reactions involving skin and other organs.
  - Risk of Acute Cardiorespiratory Failure: Patients with compromised cardiac or respiratory function may be at risk of acute cardiorespiratory failure. Caution should be exercised when

administering alglucosidase alfa to patients susceptible to fluid volume overload. Appropriate medical support and monitoring measures should be available during infusion.

- Risk of Cardiac Arrhythmia and Sudden Cardiac Death during General Anesthesia for Central Venous Catheter Placement: Caution should be used when administering general anesthesia for the placement of a central venous catheter intended for alglucosidase alfa infusion.
- Risk of Antibody Development: Patients with infantile-onset Pompe disease should have a cross-reactive immunologic material (CRIM) assessment early in their disease course and be managed by a clinical specialist knowledgeable in immune tolerance induction in Pompe disease to optimize treatment.

- Nexviazyme (avalglucosidase alfa-ngpt): see boxed warning
- Pombiliti (cipaglucosidase alfa-atga):
  - See boxed warning.
  - Embryo-Fetal Toxicity: May cause embryo-fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for at least 60 days after the last dose.
  - Risks Associated with Opfolda: Refer to the Opfolda Prescribing Information for a description of additional risks for Opfolda.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

G0138	Intravenous infusion of cipaglucosidase alfa-atga, including provider/supplier acquisition and clinical supervision of oral administration of miglustat in preparation of receipt of cipaglucosidase alfa-atga
J0219	Injection, avalglucosidase alfa-ngpt, 4 mg
J0221	Injection, alglucosidase alfa, (Lumizyme), 10 mg
J1203	Injection, cipaglucosidase alfa-atga, 5 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

E74.02	Pompe disease

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 9/10/25.

GUIDELINE UPDATE INFORMATION:

11/15/21	New Medical Coverage Guideline.
01/01/22	Revision: Added HCPCS code C9085.
04/01/22	Revision: Added HCPCS code J0219 and deleted codes C9085 and J3590.
10/15/23	Review and revision to guideline; Updated references.
04/01/24	Revision to guideline; updated position statement, dosing/administration, coding, references.
10/15/24	Review and revision to guideline; Updated references.
10/15/25	Review and revision to guideline; Updated references.