Pharmacotherapy for Pompe Disease

Medicare Advantage Medical Policy #MA-209
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Applies to all products administered or underwritten by the Health Plan, unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Blue Advantage does not cover investigational or experimental services, including any drug, device, procedure, or service provided under the investigational arm of a clinical trial or study unless mandated by the Centers for Medicare and Medicaid Services. Coverage is limited to routine services for Category A IDE studies and to devices and related services for Category B IDE studies when not supplied by the trial sponsor. Approved IDE studies are posted on www.cms.gov/medicare/coverage/evidence.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Health Plan may consider alglucosidase alfa (Lumizyme®)‡, avalglucosidase alfa-ngpt (Nexviazyme™)‡, or cipaglucosidase alfa-atga (Pombiliti™)‡ in combination with miglustat (Opfolda™)‡ for the treatment of Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency) to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for alglucosidase alfa (Lumizyme), avalglucosidase alfa-ngpt (Nexviazyme), or cipaglucosidase alfa-atga (Pombiliti) in combination with miglustat (Opfolda) will be considered when the following criteria are met for the requested drug:

- For **alglucosidase alfa (Lumizyme)** requests:
  - **Initial**
    - Patient has a diagnosis of Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency) as evidenced by documentation of GAA enzyme deficiency from any tissue source and/or 2 confirmed *GAA* gene mutations; AND
    - Patient has measurable signs of Pompe disease, such as cardiac hypertrophy, impairment in pulmonary function, or motor weakness; AND
    - For patients with late-onset (non-infantile) disease, patient meets ALL of the following criteria:
      - Patient is able to ambulate at least 130 feet without stopping; AND
      - Patient has a Forced Vital Capacity (FVC) greater than or equal to 30% predicted and less than 80% predicted; AND
      - Patient does NOT require use of invasive ventilation or noninvasive ventilation support while awake; AND
    - Baseline measurements are provided for the following:
      - Percent predicted Forced Vital Capacity (FVC); AND

- ❖ Six minute walk test (6MWT), if age appropriate; AND
- Prescriber attests that patient will be monitored for IgG antibody formation as clinically appropriate while on therapy with the requested drug; AND
- Patient is NOT using/planning to use avalglucosidase alfa-ngpt (Nexviazyme) OR cipaglucosidase alfa-atga (Pombiliti) in combination with miglustat (Opfolda) concurrently with the requested medication; AND
- Dose will not exceed 20 mg/kg intravenously every two weeks.

- **Continuation**
  - Patient has received an initial authorization for the requested drug from the plan OR has provided documentation of authorization for an active course of treatment from previous health plan; AND
  - Patient has demonstrated a beneficial response to therapy compared to pretreatment age-appropriate baseline values in ONE or more of the following:
    - ❖ Infantile-onset disease: stabilization or improvement in muscle weakness, motor function, respiratory function, cardiac involvement, FVC and/or 6-MWT; OR
    - ❖ For late-onset (non-infantile) disease: stabilization or improvement in FVC and/or 6-MWT; AND
  - For patients with Late-Onset Pompe Disease, patient meets ALL of the following criteria:
    - ❖ Patient is able to ambulate at least 130 feet without stopping; AND
    - ❖ Patient has a Forced Vital Capacity (FVC) greater than or equal to 30% predicted and less than 80% predicted; AND
    - ❖ Patient does NOT require use of invasive ventilation or noninvasive ventilation support while awake; AND
  - Patient is NOT using/planning to use avalglucosidase alfa-ngpt (Nexviazyme) OR cipaglucosidase alfa-atga (Pombiliti) in combination with miglustat (Opfolda) concurrently with the requested medication; AND
  - Dose will not exceed 20 mg/kg intravenously every two weeks.

- For **avalglucosidase alfa-ngpt (Nexviazyme)** requests**:**
  - **Initial**
    - Patient has a diagnosis of late onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency) as evidenced by GAA enzyme deficiency from any tissue source and/or 2 confirmed *GAA* gene mutations; AND
      (Note: Late-onset disease (juvenile and adult presentations) is characterized by skeletal myopathy (i.e., progressive weakness in a limb-girdle distribution), protracted course, leading to respiratory failure. Supportive findings may include electromyographic (EMG) demonstrating myopathic discharges, sometimes abundant myotonic and complex repetitive discharges, most prominent in the paraspinal muscles, and elevated serum creatinine kinase.)

- Patient is 1 year of age or older; AND
- Dosing is as follows:
  - ❖ Patient weighs 30 kg or more: 20 mg/kg of actual body weight every two weeks; OR
  - ❖ Patient weighs less than 30 kg: 40 mg/kg of actual body weight every two weeks; AND
- Patient has measurable signs of Pompe disease, such as impairment in pulmonary function or motor weakness; AND
- Patient is able to ambulate at least 130 feet without stopping and without an assistive device; AND
- Patient has a Forced Vital Capacity (FVC) greater than or equal to 30% predicted and less than or equal to 85% predicted; AND
- Patient is NOT using/planning to use alglucosidase alfa (Lumizyme) OR cipaglucosidase alfa-atga (Pombiliti) in combination with miglustat (Opfolda) concurrently with the requested medication; AND
- Patient does NOT require invasive ventilation; AND
- Patient does NOT have Pompe-specific cardiac hypertrophy; AND
- Baseline percent predicted Forced Vital Capacity (FVC) and 6-minute walk test (6MWT) measurements are provided.

- **Continuation**
  - Patient has received an initial authorization for the requested drug from the plan OR has provided documentation of authorization for an active course of treatment from previous health plan; AND
  - Patient has responded to therapy as evidenced by an improvement or stabilization in percent predicted FVC and/or 6MWT; AND
  - Dosing is as follows:
    - ❖ Patient weighs 30 kg or more: 20 mg/kg of actual body weight every two weeks; OR
    - ❖ Patient weighs less than 30 kg: 40 mg/kg of actual body weight every two weeks; AND
  - Patient is able to ambulate at least 130 feet without stopping and without an assistive device; AND
  - Patient has a Forced Vital Capacity (FVC) greater than or equal to 30% predicted and less than or equal to 85% predicted; AND
  - Patient is NOT using/planning to use alglucosidase alfa (Lumizyme) OR cipaglucosidase alfa-atga (Pombiliti) in combination with miglustat (Opfolda) concurrently with the requested medication; AND
  - Patient does NOT require invasive ventilation; AND
  - Patient does NOT have Pompe-specific cardiac hypertrophy.

- For **cipaglucosidase alfa-atga (Pombiliti)** requests:
  - **Initial (6 months)**
    - Patient has late onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency) with diagnosis established by documentation of ONE of the following:
      - ❖ Enzyme assay showing a deficiency (less than 40% of the lab specific normal mean value) of GAA activity in blood, fibroblast, or muscle tissue; OR
      - ❖ Genetic testing confirming a *GAA* gene mutation; AND

      (Note: Late-onset disease (juvenile and adult presentations) is characterized by skeletal myopathy (i.e., progressive weakness in a limb-girdle distribution), protracted course, leading to respiratory failure. Supportive findings may include electromyographic (EMG) demonstrating myopathic discharges, sometimes abundant myotonic and complex repetitive discharges, most prominent in the paraspinal muscles, and elevated serum creatinine kinase.)
    - Patient is 18 years of age or older; AND
    - Patient weighs 40 kg or more; AND
    - Patient has measurable signs of Pompe disease, such as cardiac hypertrophy, impairment in pulmonary function, or progressive proximal motor weakness; AND
    - Patient has NOT demonstrated an improvement in objective measures including both the six-minute walk test (6MWT) and forced vital capacity (FVC) after receiving one of the following for at least one year unless there is clinical evidence or patient history that suggests the alternative products will be ineffective or cause an adverse reaction to the patient:
      - ❖ alglucosidase alfa (Lumizyme); OR
      - ❖ avalglucosidase alfa-ngpt (Nexviazyme); AND
    - The medication requested will NOT be used in combination with another enzyme replacement therapy (ERT) for Pompe disease (e.g., alglucosidase alfa [Lumizyme] or avalglucosidase alfa-ngpt [Nexviazyme]); AND
    - The medication requested will be used in combination with Opfolda; AND
    - If the patient is a female of reproductive potential, provider attests that the patient is NOT currently pregnant and is willing to use effective contraception; AND
    - Patient has a 6 minute walk distance (6MWD) of greater than or equal to 75 meters; AND
    - Patient has a sitting FVC greater than or equal to 30% of the predicted value for healthy adults; AND
    - Patient does NOT require the use of invasive or noninvasive ventilation support for greater than 6 hours/day while awake; AND

- Dosing is as follows:
  - 20 mg/kg of actual body weight administered every other week as an intravenous infusion.

- **Continuation (12 months)**
  - Patient has received an initial authorization for the requested drug from the plan OR has provided documentation of authorization for an active course of treatment from previous health plan ; AND
  - Patient has experienced a positive clinical response to therapy, as evidenced by improvement or stabilization in percent predicted FVC and/or 6MWT; AND
  - The medication requested will be used in combination with Opfolda; AND
  - The medication requested will NOT be used in combination with another ERT for Pompe disease (e.g., alglucosidase alfa [Lumizyme] or avalglucosidase alfa-ngpt [Nexviazyme]); AND
  - Patient does NOT require the use of invasive or noninvasive ventilation support for greater than 6 hours/day while awake; AND
  - Dosing is as follows:
    - 20 mg/kg of actual body weight administered every other week as an intravenous infusion.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Health Plan considers the use of alglucosidase alfa (Lumizyme) when any of the following criteria are NOT met to be **not medically necessary:****

- Patient has measurable signs of Pompe disease, such as cardiac hypertrophy, impairment in pulmonary function, or motor weakness
- For patients with late-onset disease:
  - Patient is able to ambulate at least 130 feet without stopping
  - Patient has a Forced Vital Capacity (FVC) greater than or equal to 30% predicted and less than 80% predicted
  - Patient does NOT require use of invasive ventilation or noninvasive ventilation support while awake
- Baseline percent predicted Forced Vital Capacity (FVC) and age appropriate 6-minute walk test (6MWT) measurements are provided
- For continuation requests for patients with infantile onset disease: Patient has demonstrated a beneficial response to therapy compared to pretreatment age-appropriate baseline values, as evidenced by stabilization or improvement in muscle weakness, motor function, respiratory function, cardiac involvement, FVC and/or 6-MWT
- For continuation requests for patients with late-onset (non-infantile) disease: Patient has demonstrated a beneficial response to therapy compared to pretreatment age-appropriate baseline values, as evidenced by stabilization or improvement in FVC and/or 6-MWT

Based on review of available data, the Health Plan considers the use of avalglucosidase alfa-ngpt (Nexviazyme) when any of the following criteria are NOT met to be **not medically necessary:****

- Patient has measurable signs of Pompe disease, such as impairment in pulmonary function or motor weakness
- Patient is able to ambulate at least 130 feet without stopping and without an assistive device
- Patient has a Forced Vital Capacity (FVC) greater than or equal to 30% predicted and less than or equal to 85% predicted
- Patient does NOT require invasive ventilation
- Patient does NOT have Pompe-specific cardiac hypertrophy
- Baseline percent predicted Forced Vital Capacity (FVC) and 6-minute walk test (6MWT) measurements are provided
- For continuation requests specifically: Patient has responded to therapy as evidenced by an improvement or stabilization in percent predicted FVC and/or 6MWT

Based on review of available data, the Health Plan considers the use of cipaglucosidase alfa-atga (Pombiliti) when any of the following criteria are NOT met to be **not medically necessary:****

- Patient has measurable signs of Pompe disease, such as cardiac hypertrophy, impairment in pulmonary function, or progressive proximal motor weakness
- Patient has NOT demonstrated an improvement in objective measures including both the 6MWT and FVC after receiving one of the following for at least one year unless there is clinical evidence or patient history that suggests the alternative products will be ineffective or cause an adverse reaction to the patient:
  - alglucosidase alfa (Lumizyme); OR
  - avalglucosidase alfa-ngpt (Nexviazyme)
- Patient has a 6MWD of greater than or equal to 75 meters
- Patient has a sitting FVC greater than or equal to 30% of the predicted value for healthy adults
- Patient does NOT require the use of invasive or noninvasive ventilation support for greater than 6 hours/day while awake
- For continuation requests specifically: Patient has experienced a positive clinical response to therapy, as evidenced by improvement or stabilization in percent predicted FVC and/or 6MWT, and patient does NOT require the use of invasive or noninvasive ventilation support for greater than 6 hours/day while awake

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Health Plan considers the use of alglucosidase alfa (Lumizyme), avalglucosidase alfa-ngpt (Nexviazyme), or cipaglucosidase alfa-atga (Pombiliti) when the patient selection criteria are not met (with the exception of those denoted as **not medically necessary****) to be **investigational.***

Background/Overview

Nexviazyme is indicated for the treatment of patients 1 year of age and older with late-onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency). Nexviazyme is given as an intravenous infusion. For patients weighing ≥ 30 kg, the recommended dosage is 20 mg/kg every two weeks. For patients weighing < 30 kg, the recommended dosage is 40 mg/kg every two weeks.

Lumizyme is indicated for patients with Pompe disease (GAA deficiency). The recommended dosage is 20 mg/per kg body weight administered every 2 weeks as an intravenous infusion. Lumizyme has a boxed warning that anaphylactic, severe allergic and immune mediated reactions have been observed. Patients with acute underlying respiratory illness or compromised cardiac and/or respiratory function may be at risk of serious exacerbation of their cardiac or respiratory compromise during infusions; therefore, appropriate medical support should be available during infusion. Cross reactive immunologic material (CRIM) status has been shown to be associated with immunogenicity and patient response to Lumizyme. Lumizyme-treated infants with IOPD who are CRIM-negative (indicating no endogenous enzyme is detected) have shown poorer clinical response (loss of motor function, ventilator dependence, or death) in the presence of high sustained IgG Anti-alglucosidase alfa antibody (ADA) titers and positive inhibitory antibodies compared to CRIM-positive infants. However, high and sustained ADA titers have also occurred in a limited number of CRIM-positive patients, generally with very low endogenous enzyme. According to the prescribing information for Lumizyme, patients with IOPD should have a CRIM assessment early in their disease course and be managed by a specialist knowledgeable in immune tolerance induction in Pompe disease to optimize treatment. Some Lumizyme-treated patients who developed high sustained IgG ADA titers had reduced efficacy. Some Lumizyme-treated patients with high IgG ADA titers had a higher incidence of infusion-associated reactions. According to the prescribing information, baseline serum ADA sample collection prior to the first Lumizyme infusion is strongly encouraged. For patients with IOPD, regular ADA monitoring during the first year of treatment (example: every 3 months) is recommended. For patients with LOPD, ADA should be monitored within six months of Lumizyme initiation with subsequent monitoring as clinically warranted based on safety and efficacy considerations.
Pombiliti and Opfolda are indicated in combination for the treatment of adult patients with late-onset Pompe disease weighing ≥ 40 kg and who are not improving on their current ERT. The recommended dosage of Pombiliti is 20 mg/kg, based on actual body weight, administered once every other week as an intravenous infusion. The recommended dosage of Opfolda for patients weighing ≥ 50 kg is 260 mg by mouth once every other week. For patients weighing > 40 kg to < 50 kg, the dose is 195 mg by mouth once every other week. Opfolda must be administered 1 hour before the intravenous administration of Pombiliti.

Pompe disease, also known as lysosomal acid alpha-glucosidase (GAA) deficiency, is an autosomal recessive disorder which leads to an accumulation of glycogen in lysosomes and cytoplasm, ultimately leading to tissue destruction. The diagnosis of Pompe disease is established by demonstrating decreased acid alpha-glucosidase activity in blood, fibroblasts, or muscle tissue; or by genetic testing. There are two main types of Pompe disease which are classified based on disease

severity and the age at which symptoms appear: infantile-onset Pompe disease (IOPD) and late-onset Pompe Disease (LOPD). Infantile onset typically presents within the first few months of life and is characterized by hypotonia, difficulty feeding, and cardiopulmonary failure. If left untreated, death often occurs in the first few months of life. Late onset Pompe disease may present any time after 12 months of age, has a more variable clinical course, and is characterized by skeletal myopathy and eventual respiratory failure without cardiomyopathy. Given that this condition results from a genetic disorder, which ultimately leads to an enzyme deficiency, treatment focuses on replacing the missing enzymes. Currently, there are three FDA-approved enzyme replacement therapies for Pompe disease on the market: Lumizyme, Nexviazyme, and Pombiliti. Of note, Pombiliti is only FDA-approved for use in combination with Opfolda. Pombiliti, an intravenous ERT, and Opfolda, an oral enzyme stabilizer, received separate FDA approvals and have their own prescribing information but share the same indication and requirement for use in combination in patients not improving on their current ERT.

Lumizyme carries approval for both the infantile and late onset varieties of Pompe disease, while Nexviazyme and Pombiliti plus Opfolda only carry approval for late onset Pompe disease. Nexviazyme and Lumizyme are structurally and mechanistically similar and contain the same enzyme needed for replacement in Pompe disease. Clinical trials comparing Nexviazyme and Lumizyme in late onset Pompe disease showed non-inferiority and non-superiority of Nexviazyme as compared to Lumizyme. Pombiliti in combination with Opfolda is the first two drug regimen intended to improve uptake of the exogenous enzyme through enzyme stabilization but whether this improves efficacy when compared to Lumizyme, has not been established in clinical trials. Clinical trials comparing Pombiliti plus Opfolda to Nexviazyme have not been conducted. The safety of Lumizyme, Nexviazyme, and Pombiliti in combination with Opfolda is considered similar.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Lumizyme is indicated for patients with Pompe disease (GAA deficiency). It was approved in 2010.

Nexviazyme is indicated for the treatment of patients 1 year of age and older with late-onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency). It was approved in 2021.

Pombiliti was approved in 2023 for use in combination with Opfolda for the treatment of adult patients with LOPD weighing ≥ 40 kg and who are not improving on their current ERT.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

Lumizyme
The safety and effectiveness of alglucosidase alfa in the treatment of patients with IOPD were assessed in 57 treatment-naive infantile-onset Pompe disease patients, aged 0.2 month to 3.5 years at first alglucosidase alfa infusion, in three separate open-label, single-arm clinical trials (Trials 1, 2, and 3). Safety and efficacy of alglucosidase alfa in the treatment of patients with LOPD were assessed in a separate randomized, double-blind, placebo-controlled trial (Trial 4).

Trial 1 (Patients with IOPD)
Trial 1 was an international, multicenter, open-label, clinical trial of 18 patients with IOPD. Patients were randomized 1:1 to receive either 20 mg/kg or 40 mg/kg of intravenous 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 trial 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 patients with IOPD with similar age and disease severity. In the historical cohort, 61 untreated patients with IOPD diagnosed by age 6 months 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 trial 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 of 118 g/m, range 45 to 193 g/m). However, the magnitude of the decrease in LVMI did not correlate with the clinical outcome measure of ventilator-free survival.

Trial 2 (Patients with IOPD)
Trial 2 was an international, multicenter, non-randomized, open-label clinical trial that enrolled 21 patients with IOPD aged 3 months to 3.5 years at first infusion. Eighteen patients were CRIM positive and 3 patients were CRIM negative. All patients received intravenous 20 mg/kg alglucosidase alfa every other week for up to 104 weeks. Five of 21 patients were receiving invasive ventilatory support at the time of first infusion. The primary outcome measure was the proportion of patients alive at the conclusion of treatment. At the 52-week interim analysis, 16 of 21 patients were alive. Sixteen patients were free of invasive ventilatory support at the time of first infusion; of these,

4 died, 2 required invasive ventilatory support, and 10 were free of invasive ventilatory support after 52 weeks of treatment. For the 5 patients who were receiving invasive ventilatory support at baseline, 1 died, and 4 remained on invasive ventilatory support at Week 52.

Trial 3 (Patients with IOPD)
Trial 3 was an open-label, single-center trial in 18 patients with IOPD who had a confirmed diagnosis of Pompe disease as identified through a newborn screening program. All patients were CRIM positive. Patients were treated with intravenous alglucosidase alfa prior to 6 months of age (0.2 to 5.8 months at first infusion). Sixteen patients reached 18 months of age at the time of analysis, and all (100%) were alive without invasive ventilator support.

Trial 4 (Patients with LOPD)
The safety and efficacy of alglucosidase alfa were assessed in 90 patients with LOPD, 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 of intravenous alglucosidase alfa (n = 60) or intravenous placebo (n = 30) every other week for 78 weeks (18 months). The youngest alglucosidase alfa-treated patient was 16 years of age, and the youngest placebo-treated patient was 10 years of age. 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 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 trial entry, the mean percent predicted FVC in the sitting position among all patients was about 55%. After 78 weeks, the mean percent 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 percent predicted FVC in the alglucosidase alfa-treated patients was observed. At trial 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).

Nexviazyme
Study 1 was a randomized, double-blinded, multinational, multicenter trial comparing the efficacy and safety of Nexviazyme to Lumizyme in 100 treatment-naive patients with late onset Pompe Disease (LOPD). 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 Nexviazyme or Lumizyme administered intravenously once every two weeks for 49 weeks. The trial included an open-label, long-term, follow-up phase of up to 5 years, in which patients in the Lumizyme arm were switched to

Nexviazyme treatment. Of the 100 randomized patients, 52 were males, the baseline median age was 49 years old (range from 16 to 78), median baseline weight was 76.4 kg (range from 38 to 139 kg), median length of time since diagnosis was 6.9 months (range from 0.3 to 328.4 months), mean age at diagnosis was 46.4 years old (range from 11 to 78), mean forced vital capacity (FVC, measured as % predicted) at baseline was 62.1% (range from 32 to 85%), and mean 6 minute walk test (6MWT) at baseline was 388.9 meters (range from 118 to 630 meters). The primary endpoint of Study 1 was the change in FVC (% predicted) in the upright position from baseline to Week 49. At Week 49, the least squares (LS) mean change in FVC (% predicted) for patients treated with Nexviazyme and Lumizyme was 2.9% and 0.5%, respectively. The estimated treatment difference was 2.4% (95% CI: -0.1, 5.0) favoring Nexviazyme. However, it should be clearly noted that there was a noninferiority margin of 1.1% ($p = 0.0074$). Statistical superiority of Nexviazyme over Lumizyme was not achieved ($p = 0.06$).

Pombiliti in combination with Opfolda
Trial 1 was a randomized, double-blind, active-controlled, international, multi-center clinical trial in patients 18 years of age and older diagnosed with LOPD. Patients were randomized 2:1 to receive Pombiliti (20 mg/kg by intravenous infusion) in combination with Opfolda (260 mg orally for those ≥ 50 kg or 195 mg orally for those ≥ 40 kg to < 50 kg) or a non-U.S.-approved alglucosidase alfa product with placebo every other week for 52 weeks. The efficacy population included a total of 123 patients of whom 95 (77%) had received prior treatment with U.S.-approved alglucosidase alfa or a non-U.S.-approved alglucosidase alfa product (ERT-experienced) and 28 (23%) were ERT-naïve. More than two thirds (n = 64, 67%) of ERT-experienced patients had been on ERT treatment for more than 5 years prior to entering Trial 1 (mean of 7.4 years). Demographics, baseline sitting FVC (% predicted), and 6MWD were generally similar between the 2 treatment groups. Key efficacy endpoints included assessment of sitting FVC (% predicted) and 6 MWD. Patients treated with Pombiliti in combination with Opfolda showed a mean change in sitting FVC from baseline at Week 52 of -1.1% as compared with patients treated with a non-U.S. approved alglucosidase alfa product with placebo of -3.3%; the estimated treatment difference was 2.3% (95% CI: 0.02, 4.62). The ERT-experienced patients treated with Pombiliti in combination with Opfolda showed a numerically favorable change in sitting FVC from baseline at Week 52. Patients treated with Pombiliti in combination with Opfolda walked on average 21 meters farther from baseline as compared to those treated with a non-U.S.-approved alglucosidase alfa product with placebo who walked 8 meters farther from baseline; the estimated treatment difference was 14 meters (95% CI: -1, 28). The ERT-experienced patients treated with Pombiliti in combination with Opfolda showed a numerically favorable change in 6MWD from baseline at Week 52.

References

1. Nexviazyme [package insert]. Genzyme Corporation. Cambridge, Massachusetts. Updated September 2023.
2. Lysosomal acid alpha-glucosidase deficiency (Pompe disease, glycogen storage disease II, acid maltase deficiency). UpToDate. Updated September 2021.
3. Nexviazyme New Drug Review. IPD Analytics. August 2021.

4. Pombiliti and Opfolda New Drug Review. IPD Analytics. October 2023.
5. Pombiliti and Opfolda Drug Evaluation. Express Scripts. October 2023.
6. Pombiliti [package insert]. Amicus Therapeutics Inc. Philadelphia, Pennsylvania. Updated July 2024.
7. Kishnani PS, Diaz-Manera J, Toscano A, et al. Efficacy and Safety of Avalglucosidase Alfa in Patients With Late-Onset Pompe Disease After 97 Weeks: A Phase 3 Randomized Clinical Trial. *JAMA Neurol.* 2023;80(6):558–567.
8. Ploeg AT, Clemens PR, et al. A randomized study of alglucosidase alfa in late-onset Pompe's disease N Engl J Med, 362 (2010), pp. 1396-1406.
9. Lumizyme [package insert]. Genzyme Corporation. Cambridge, Massachusetts. Updated December 2024.

Policy History

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03/17/2026 UM Committee review and approval. New policy.
Next Scheduled Review Date: 03/2027

Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No Codes
HCPCS	G0138, J0219, J1203, J0221
ICD-10 Diagnosis	All Related Diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the Health Plan Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Health Plan recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

NOTICE: All codes listed on the Medical Policy require prior authorization. This ensures appropriate utilization and alignment with current clinical guidelines.

NOTICE: If an authorization for an ongoing course of treatment has been provided to a member and the member changes from one health plan to another health plan (e.g., a member moves from carrier A to Blue Advantage), Blue Advantage may honor the previous health plan's authorization for the same service under the same type of in-network benefit for a 90-day transition period. Documentation of the authorization for the ongoing course of treatment from the previous health plan must be provided to us by the member or their provider and the services provided for the course of treatment must otherwise be a covered service under the Blue Advantage health plan.

Medicare Advantage Members

Established coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses coverage for a specific service, refer to the Medicare Coverage Database at the following link: https://www.cms.gov/medicare-coverage-database/search.aspx. You may wish to review the Guide to the MCD Search here: https://www.cms.gov/medicare-coverage-database/help/mcd-bene-help.aspx.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria may be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of this internal coverage criteria.