

## Pharmacotherapy for Pompe Disease

**Policy # 00771**

Original Effective Date: 02/14/2022

Current Effective Date: 03/01/2026

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

### 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 Company may consider alglucosidase alfa (Lumizyme<sup>®</sup>)<sup>‡</sup>, avalglucosidase alfa-ngpt (Nexviazyme<sup>™</sup>)<sup>‡</sup>, or cipaglucosidase alfa-atga (Pombiliti<sup>™</sup>)<sup>‡</sup> in combination with miglustat (Opfolda<sup>™</sup>)<sup>‡</sup> 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), cipaglucosidase alfa-atga (Pombiliti), and miglustat (Opfolda) will be considered when the following criteria are met for the requested drug:

- For **alglucosidase alfa (Lumizyme)** requests:
  - **Initial Authorization**
    - 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  
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary\*\* if not met.)*
    - 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)  $\geq 30\%$  predicted and  $< 80\%$  predicted; AND
      - ❖ Patient does NOT require use of invasive ventilation or noninvasive ventilation support while awake; AND  
*(Note: These specific patient selection criteria are an additional Company requirement for coverage eligibility and will be denied as not medically necessary\*\* if not met.)*

## Pharmacotherapy for Pompe Disease

Policy # 00771

Original Effective Date: 02/14/2022

Current Effective Date: 03/01/2026

- Baseline measurements are provided for the following:
  - ❖ Percent predicted Forced Vital Capacity (FVC); AND
  - ❖ Six minute walk test (6MWT), if age appropriate; AND

*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary\*\* if not met.)*
- 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; 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

*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary\*\* if not met.)*
  - 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)  $\geq$  30% predicted and  $<$  80% predicted; AND
    - ❖ Patient does NOT require use of invasive ventilation or noninvasive ventilation support while awake; AND

*(Note: These specific patient selection criteria are an additional Company requirement for coverage eligibility and will be denied as not medically necessary\*\* if not met)*
  - 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.

Policy # 00771

Original Effective Date: 02/14/2022

Current Effective Date: 03/01/2026

- For **avalglucosidase alfa-ngpt (Nexviazyme)** requests:
  - **Initial Authorization**
    - 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:
      - ❖  $\geq 30$  kg: 20 mg/kg of actual body weight every two weeks; OR
      - ❖  $< 30$  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  
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary\*\* if not met.)*
    - Patient is able to ambulate at least 130 feet without stopping and without an assistive device; AND  
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary\*\* if not met.)*
    - Patient has a Forced Vital Capacity (FVC)  $\geq 30\%$  predicted and  $\leq 85\%$  predicted; AND  
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary\*\* if not met.)*
    - 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  
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary\*\* if not met.)*
    - Patient does NOT have Pompe-specific cardiac hypertrophy; AND  
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary\*\* if not met.)*

## Pharmacotherapy for Pompe Disease

Policy # 00771

Original Effective Date: 02/14/2022

Current Effective Date: 03/01/2026

- Baseline percent predicted Forced Vital Capacity (FVC) and 6 minute walk test (6MWT) measurements are provided.

*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary\*\* if not met.)*

- **Continuation**

- Patient has received an initial authorization; AND
- Patient has responded to therapy as evidenced by an improvement or stabilization in percent predicted FVC and/or 6MWT; AND

*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary\*\* if not met.)*

- Dosing is as follows:

- ❖  $\geq 30$  kg: 20 mg/kg of actual body weight every two weeks; OR

- ❖  $< 30$  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

*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary\*\* if not met.)*

- Patient has a Forced Vital Capacity (FVC)  $\geq 30\%$  predicted and  $\leq 85\%$  predicted; AND

*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary\*\* if not met.)*

- 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

*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary\*\* if not met.)*

- Patient does NOT have Pompe-specific cardiac hypertrophy.

*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary\*\* if not met.)*

Policy # 00771

Original Effective Date: 02/14/2022

Current Effective Date: 03/01/2026

- For **cipaglucosidase alfa-atga (Pombiliti)** requests:
  - **Initial** Authorization (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 (< 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

*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary\*\* if not met.)*

    - 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

*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary\*\* if not met.)*
    - 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 Opfoda; 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

## Pharmacotherapy for Pompe Disease

Policy # 00771

Original Effective Date: 02/14/2022

Current Effective Date: 03/01/2026

- Patient has a 6 minute walk distance (6MWD) of  $\geq 75$  meters; AND  
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary\*\* if not met.)*
- Patient has a sitting FVC  $\geq 30\%$  of the predicted value for healthy adults; AND  
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary\*\* if not met.)*
- Patient does NOT require the use of invasive or noninvasive ventilation support for  $> 6$  hours/day while awake; AND  
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary\*\* if not met.)*
- Dosing is as follows:
  - ❖ 20 mg/kg of actual body weight administered every other week as an intravenous infusion.

### ○ Continuation

- Patient has received an initial authorization; AND
- Patient has experienced a positive clinical response to therapy, as evidenced by improvement or stabilization in percent predicted FVC and/or 6MWT; AND  
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary\*\* if not met.)*
- 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  $> 6$  hours/day while awake; AND  
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary\*\* if not met.)*
- Dosing is as follows:
  - ❖ 20 mg/kg of actual body weight administered every other week as an intravenous infusion.

Policy # 00771

Original Effective Date: 02/14/2022

Current Effective Date: 03/01/2026

- For **miglustat (Opfolda)** requests:
  - **Initial** Authorization (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 (< 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

*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary\*\* if not met.)*

    - 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

*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary\*\* if not met.)*
    - 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
    - The medication requested will be used in combination with Pombiliti; 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

## Pharmacotherapy for Pompe Disease

Policy # 00771

Original Effective Date: 02/14/2022

Current Effective Date: 03/01/2026

- Patient has a 6 minute walk distance (6MWD) of  $\geq 75$  meters; AND  
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary\*\* if not met.)*
  - Patient has a sitting FVC  $\geq 30\%$  of the predicted value for healthy adults; AND  
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary\*\* if not met.)*
  - Patient does NOT require the use of invasive or noninvasive ventilation support for  $> 6$  hours/day while awake;  
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary\*\* if not met.)*
  - **Continuation**
    - Patient has received an initial authorization; AND
    - Patient has experienced a positive clinical response to therapy, as evidenced by improvement or stabilization in percent predicted FVC and/or 6MWT; AND  
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary\*\* if not met.)*
    - The medication requested will be used in combination with Pombiliti; 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  $> 6$  hours/day while awake;  
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary\*\* if not met.)*
- OR**
- Patient has a diagnosis of **Niemann-Pick Disease type C**.  
*(Note: Authorizations for miglustat (Opfolda) for the treatment of Niemann-Pick Disease type C will be approved for ONE year.)*

## When Services Are Considered Not Medically Necessary

Based on review of available data, the Company 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



## Pharmacotherapy for Pompe Disease

Policy # 00771

Original Effective Date: 02/14/2022

Current Effective Date: 03/01/2026

- For patients with late-onset disease:
  - Patient is able to ambulate at least 130 feet without stopping
  - Patient has a Forced Vital Capacity (FVC)  $\geq$  30% predicted and  $<$  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 Company 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)  $\geq$  30% predicted and  $\leq$  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 Company considers the use of cipaglucosidase alfa-atga (Pombiliti) or miglustat (Opfolda) 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  $\geq$  75 meters
- Patient has a sitting FVC  $\geq$  30% of the predicted value for healthy adults
- Patient does NOT require the use of invasive or noninvasive ventilation support for  $>$  6 hours/day while awake

Policy # 00771

Original Effective Date: 02/14/2022

Current Effective Date: 03/01/2026

- 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 > 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 Company considers the use of alglucosidase alfa (Lumizyme), avalglucosidase alfa-ngpt (Nexviazyme), cipaglucosidase alfa-atga (Pombiliti), or miglustat (Opfolda) 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  $\geq 30$  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.

## Pharmacotherapy for Pompe Disease

Policy # 00771

Original Effective Date: 02/14/2022

Current Effective Date: 03/01/2026

Pombiliti and Opfolda are indicated in combination for the treatment of adult patients with late-onset Pompe disease weighing  $\geq 40$  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  $\geq 50$  kg is 260 mg by mouth once every other week. For patients weighing  $\geq 40$  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.

Policy # 00771

Original Effective Date: 02/14/2022

Current Effective Date: 03/01/2026

## **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  $\geq 40$  kg and who are not improving on their current ERT.

Opfolda was approved in 2023 for use in combination with Pombiliti for the treatment of adult patients with LOPD weighing  $\geq 40$  kg and who are not improving on their 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-naïve 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

Policy # 00771

Original Effective Date: 02/14/2022

Current Effective Date: 03/01/2026

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

Policy # 00771

Original Effective Date: 02/14/2022

Current Effective Date: 03/01/2026

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-naïve 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  $\geq 50$  kg or 195 mg orally for those  $\geq 40$  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

## Pharmacotherapy for Pompe Disease

Policy # 00771

Original Effective Date: 02/14/2022

Current Effective Date: 03/01/2026

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 August 2021.
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. Opfolda [package insert]. Amicus Therapeutics Inc. Philadelphia, Pennsylvania. Updated October 2023.
7. Pombiliti [package insert]. Amicus Therapeutics Inc. Philadelphia, Pennsylvania. Updated October 2023.
8. 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.
9. 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.
10. Lumizyme [package insert]. Genzyme Corporation. Cambridge, Massachusetts. Updated December 2024.

## **Policy History**

Original Effective Date: 02/14/2022

Current Effective Date: 03/01/2026

01/06/2022	Medical Policy Committee review
01/12/2022	Medical Policy Implementation Committee approval. New policy.
03/21/2022	Coding update
01/05/2023	Medical Policy Committee review
01/11/2023	Medical Policy Implementation Committee approval. No change to coverage.
01/04/2024	Medical Policy Committee review
01/10/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/27/2024	Coding update

## Pharmacotherapy for Pompe Disease

Policy # 00771

Original Effective Date: 02/14/2022

Current Effective Date: 03/01/2026

- 04/04/2024 Medical Policy Committee review
- 04/10/2024 Medical Policy Implementation Committee approval. Added new drugs, Pombiliti and Opfolda, with relevant criteria, background information, and rationale. Changed title from “avalglucosidase alfa-ngpt (Nexviazyme)” to “Pharmacotherapy for Pompe Disease.” Updated Nexviazyme criteria to include Pombiliti as additional ERT option.
- 04/03/2025 Medical Policy Committee review
- 04/09/2025 Medical Policy Implementation Committee approval. Removed Nexviazyme criterion requiring that the patient has not failed therapy with Lumizyme. Added coverage criteria for Opfolda for the diagnosis of Niemann-Pick Disease type C.
- 12/04/2025 Medical Policy Committee review
- 12/10/2025 Medical Policy Implementation Committee approval. Added Lumizyme to the policy with relevant criteria, background information and rationale. Removed Nexviazyme criterion requiring clinical evidence or patient history suggesting Lumizyme will be ineffective or cause an adverse reaction to the patient.

Next Scheduled Review Date: 12/2026

## **Coding**

*The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)<sup>‡</sup>, copyright 2024 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.*

*The responsibility for the content of Louisiana Blue Medical Policy Coverage Guidelines is with Louisiana Blue and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Louisiana Blue Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Louisiana Blue Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.*

CPT is a registered trademark of the American Medical Association.



## Pharmacotherapy for Pompe Disease

Policy # 00771

Original Effective Date: 02/14/2022

Current Effective Date: 03/01/2026

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 Delete codes effective 05/01/2025: J3490, J3590, C9399 Add code effective 1/1/2026: 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.

## Pharmacotherapy for Pompe Disease

Policy # 00771

Original Effective Date: 02/14/2022

Current Effective Date: 03/01/2026

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

**NOTICE:** If the Patient's health insurance contract contains language that differs from the BCBSLA 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 Company 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.