© Copyright 2021 Oregon State University. All Rights Reserved

**Drug Use Research & Management Program**
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
**Phone** 503-947-5220 | **Fax** 503-947-2596

# Drug Class Update with New Drug Evaluation: Drugs for Pompe Disease

**Date of Review:** February 2022

**Date of Last Review:** April 2021
**Dates of Literature Search:** 4/1/2021- 11/05/2021
**Generic Name:** avalglucosidase alfa-ngpt
**Brand Name (Manufacturer):** Nexviazyme™ (Genzyme Corporation)
**Dossier Received:** yes

**Current Status of PDL Class:**
See **Appendix 1**.

**Purpose for Class Update:**
The purpose of the Pompe Disease drug class update is to evaluate new literature published since the last review and to evaluate the efficacy and safety of avalglucosidase alfa, a new formulation of recombinant human acid alfa glucosidase (GAA).

**Research Questions:**
1. What is the efficacy and effectiveness of alglucosidase alfa or avalglucosidase alfa in reducing symptoms, improving functional outcomes, and improving mortality in patients with Pompe disease?
2. What are the harms of alglucosidase alfa or avalglucosidase alfa treatment in Pompe disease patients?
3. Are there subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) that would benefit or be harmed from alglucosidase alfa or avalglucosidase alfa therapy?

**Conclusions:**
- The safety and efficacy of avalglucosidase alfa was assessed in one phase 3, randomized, double-blind multinational, multicenter non-inferiority (NI) trial in enzyme replacement therapy (ERT)-naïve late-onset Pompe disease (LOPD) patients aged 16 years and older.[1,2] In the 49-week study, patients (n=100) were randomly allocated in a 1:1 ratio to either avalglucosidase alfa 20 mg/kg (n=51) or alglucosidase alfa at 20 mg/kg every other week (n=49).[1,2] The study is unpublished so risk of bias could not be fully assessed.
- The primary outcome was least square means (LSM) change in percent of predicted forced vital capacity (FVC) in the upright position from baseline to 49 weeks.[1,2] The NI margin for the lower bound of the two-sided 95% confidence interval (CI) for the difference between the two treatment arms was set at -1.1%.[1] At 49 weeks, the estimated mean change from baseline in percent predicted FVC was higher in the avalglucosidase alfa arm (2.9%) versus alglucosidase alfa (0.5%) with an estimated treatment difference of 2.4% (95% CI -0.1 to 5.0; p=0.06) in favor of avalglucosidase alfa.[1,2] The trial met noninferiority for the primary efficacy endpoint but did not achieve statistical superiority.[1]

Author: David Engen, PharmD

- Clinically relevant secondary endpoints evaluated the estimated treatment difference of distance walked in the 6-minute walk test (6MWT) and health-related quality of life as measured by the 12-item short form health survey (SF-12).[1,2] The estimated mean change from baseline to week 49 in the 6MWT was higher in the avalglucosidase alfa arm (32.2 meters) versus avalglucosidase alfa (2.2 meters) with an estimated treatment difference of 30.0 meters (95% CI 1.3 to 58.7; p=0.04) in favor of avalglucosidase alfa.[1,2] There were no statistically significant differences between groups in the SF-12 score at week 49 compared to baseline.[1]
- The most common adverse events that occurred during treatment over 49 weeks in the avalglucosidase and alglucosidase groups, respectively, were headache (22% vs. 33%), fatigue (18% vs. 14%), diarrhea (12% vs. 16%), nausea (12% vs. 14%), arthralgia (10% vs. 16%), dizziness (10% vs. 8%), and myalgia (10% vs. 14%).[1,2]
- FDA labeling has a black boxed warning (BBW) for the possibility of life-threatening hypersensitivity reactions including anaphylaxis, infusion-associated reactions (IARs) and risk of acute cardiorespiratory failure in susceptible patients.[2] More frequent monitoring of vital signs should be performed during infusion for susceptible patients.[2] If severe IAR occurs, therapy should be immediately discontinued and appropriate medical treatment initiated.[2] Those with higher risk for IARs include patients with:
  - -advanced Pompe disease
  - -susceptibility to fluid volume overload
  - -acute underlying respiratory illness
  - -compromised cardiac or respiratory function necessitating fluid restriction.[2]
- There is low-quality evidence of no difference between alglucosidase alfa 20 mg/kg and 40 mg/kg in safety and effectiveness for the treatment of IOPD based on one systematic review.[3]
- There is insufficient evidence to evaluate the use of avalglucosidase alfa in the treatment of specific subpopulations based on age, gender, race, ethnicity, comorbidities, disease duration or severity.

**Recommendations:**
- Add avalglucosidase alfa to the Lysosomal Storage Disorders preferred drug list (PDL) class and designate as non-preferred.
- Update prior authorization criteria for Pompe Disease drugs and incorporate avalglucosidase alfa clinical criteria to ensure appropriate use.
- After costs were evaluated in executive session, no additional changes were made to the PDL.

**Summary of Prior Reviews and Current Policy**

Pharmacotherapy for Pompe disease was last reviewed by the Pharmacy and Therapeutics (P & T) meeting in April of 2021. At that time, alglucosidase alfa was added to the Lysosomal Storage Disorders PDL class and remained non-preferred. Prior authorization (PA) criteria was implemented for alglucosidase alfa to ensure medically appropriate use. Additional PA revisions were approved by the P & T Committee to ensure safe and appropriate utilization of alglucosidase alfa, including the recommendation that newly started patients be monitored for IgG antibody formation every 3 months for 2 years and then annually thereafter per manufacturer labeling.

**Background:**

Pompe disease, also known as glycogen storage disease type II or acid maltase deficiency, is a rare inherited, degenerative disease caused by pathogenic alpha-glucosidase gene variants which result in a deficiency of the lysosomal alpha glucosidase (GAA).[4,5] GAA mutations lead to a nonfunctional GAA enzyme and lysosomal accumulation of glycogen stored in skeletal and cardiac muscle as well as other tissues.[4,5] Accumulation of glycogen due to GAA deficiency manifests

in a wide disease spectrum from mild progressive myopathy without cardiac involvement to profound muscle weakness and hypotonia, respiratory distress, and hypertrophic cardiomyopathy. [4,5] Generally, early deficiencies in GAA activity result in rapid progression of disease and decline of motor function.[4,5] Although Pompe disease typically presents within the first 2 months of life, it can also manifest beyond infancy. [4,5] Early-onset Pompe disease with symptoms of cardiomyopathy, if left untreated, typically results in death from cardiorespiratory failure by the second year of life. [4,5]

It is estimated that Pompe disease affects roughly 1:40,000 people worldwide. In the United States, prevalence of Pompe is estimated between 1 in 21,979 and 1 in 9,625 births, while African Americans may represent a rate as high as 1:14,000.[6,7,8] Risk factors for development of Pompe disease include family history of glycogen storage disease (Type 2) where, at conception, siblings of a patient have a 25% chance of disease development.[8] A claims-based review from 1/1/2020-12/31/2020 revealed 15 patients in the Oregon Health Plan (OHP) population with a Pompe disease diagnosis, 3 of whom were Fee-for-Service (FFS) members. Pompe disease is a funded condition on line 147 (glycogenosis) of the Health Evidence Review Commission (HERC) prioritized list of health services. In Oregon, newborn screening (NBS) for Pompe disease is available through the Northwest Regional Newborn Bloodspot Screening (NWRNBS) Program.[9]

Clinical presentation of Pompe disease differs based on the age of onset, type of organs involved, progression rate, and severity.[10,11] Infantile-onset Pompe Disease (IOPD) generally presents before 12 months of age (median age ~4 months), with rapid progression of symptoms such as muscle weakness, respiratory distress, and cardiac complications.[10] The hallmark of IOPD is cardiomyopathy although the mechanism is poorly understood. Most IOPD patients die of cardiac and respiratory failure without achievement of motor milestones such as turning over, sitting, or crawling. [10,11] Late-onset Pompe disease (LOPD) describes individuals who generally present after 12 months and without cardiac involvement.[10,11] The partial loss of GAA activity in LOPD results in less pronounced muscle dysfunction and slower overall decline compared to IOPD, although individuals may still eventually require a wheelchair and other assistive devices.[10,11] Osteoporosis, scoliosis, small-fiber neuropathy, sleep apnea, hearing loss, dysphagia, impaired gastric function, fatigue, and risk of cerebral aneurisms and cardiac arrhythmia are also common in LOPD patients.[12] Respiratory dysfunction from intercostal and accessory muscle decline commonly leads to mortality through respiratory failure. [4,5] Male gender and an earlier age of onset may predict a more rapid disease course in LOPD patients.[10,11] There have been proposals to classify LOPD into a "childhood" form if symptom onset presents between birth and adolescence without progressive cardiac hypertrophy, and an "adult" form with symptom onset from adolescence into late adulthood. [10,11] However, with LOPD able to manifest at any age after infancy, a classification scheme based on age is difficult.[11] **Table 1** highlights some general features which distinguish IOPD from LOPD.

**Table 1:** General Characteristics of IOPD versus LOPD[10,11]

| **IOPD** | **LOPD** |
|---|---|
| Onset ≤12 months old **with** cardiomyopathy | Onset <12 months **without** cardiomyopathy or Onset >12 months into adulthood |
| Typical age at diagnosis: <1-year-old | Typical age at diagnosis: roughly 40 years old |
| Alfa glucosidase enzyme activity <1% normal (Complete deficiency) | Alfa glucosidase enzyme activity 2%-40% of normal (Partial deficiency) |
| Rapid disease progression | Slow progression |
| Generalized muscle weakness | Proximal (core) muscle weakness |
| Respiratory distress | Respiratory insufficiency |
| Death <2 years old if untreated | Death 55 years (range 23-77 years) if untreated |

The GAA gene is located on chromosome 17q25 and hundreds of variations have been identified.[8,13] Although the majority of GAA gene mutations have proven to be pathogenic, there are also at least 67 nonpathogenic GAA mutations and 25 variations with an unknown effect.[8,13] The clinical course of disease depends upon the type of mutation and subsequent residual GAA activity.[14] Numerous mutations have been found common to patients of certain ethnicities. Many Taiwanese patients with Pompe disease share mutations in p.Asp645Glu.[15] In African-American patients, the p.Arg854Ter mutation can be traced back to populations of North Central Africa.[16] One study traced two separate cases of early Pompe disease to a small region in Mexico where the individuals shared the same c.1987delC frameshift mutation.[17] The GAA mutation most frequently found among Caucasian children and adults with Pompe disease is c.-32-13T>G.[18] However, there are at least two known variants (c.1726G>A and c.2065G>A) that cause a pseudodeficiency where low levels of GAA activity are found with no evidence of clinical disease.[19,20] This pseudodeficiency has been noted at a high frequency in the Asian population which may increase false-positive newborn screening results.[19,20] Typically, diagnosis of Pompe is accomplished by an acid alpha-glucosidase activity test obtained from dried blood spots and may be confirmed by a second test or by observance of 2 disease-causing GAA alleles via gene mutation analysis.[10,11] Less than 1% of normal GAA gene activity, or complete deficiency, is consistent with classic IOPD while partial deficiency (2%-40% of normal activity) is characteristic of non-classic IOPD and LOPD.[10,11]

Treatment for Pompe disease may include a variety of strategies which depend upon patient age, stage, genetic factors, and clinical manifestations.[10,11,13,21] Management usually requires a multidisciplinary approach with expertise in cardiology, pulmonology, metabolic disease, neurology, rehabilitation services, and nutrition support. [10,11,13] Respiratory, motor, and nutritional assessments are needed at regular intervals to track disease activity and monitor progress. [10,11,13] Some studies suggest that enhanced nutrition and exercise may help slow muscle function decline in LOPD patients. [10,11,13] A cardiology evaluation with chest X-rays and echocardiography may be of value to monitor left ventricular mass index (LMVI) and risk of sudden cardiac death.[10,11,13,22] Respiratory surveillance is accomplished through regular pulmonary function tests (PFTs) to ensure airway integrity.[10,11,13] For those patients with a need for respiratory support, supplemental oxygen or non-invasive ventilatory support may be warranted.[10,11,13] Assessment of musculoskeletal changes and function via magnetic resonance imaging (MRI), periodic scoliosis tests, and bone mineral density scans are also suggested.[10,11,13] Annual hearing evaluations and renal function studies, as well as periodic nutritional/feeding assessments are a crucial component in the effective management of patients with Pompe disease. [10,11,13]

Enzyme replacement therapy (ERT) has been studied for many clinical outcomes in Pompe disease including mortality, respiratory function, ventilator dependence, and walking distance, but its effectiveness for all types and stages of disease has shown mixed results.[23] In IOPD, ERT is typically started upon diagnosis or once symptomatic Pompe disease is recognized.[10,11,13] The benefit of ERT in LOPD patients is less clear and may be dependent upon clinical signs, symptoms and rate of progression.[10,11,13] Although ERT has been a major breakthrough in prolonging survival, it is not a cure and it has significant limitations such as the potential for severe infusion-related reactions and/or extremely high antibody titers with negative effects on treatment efficacy.[23]

Almost all Pompe patients develop antibodies to exogenous ERT, but the response is especially problematic in those IOPD patients with no endogenous GAA. IOPD patients with two GAA mutations and unable to synthesize the GAA enzyme are categorized as cross-reactive immunological material (CRIM)-negative.[24] LOPD patients and GAA-deficient IOPD patients with at least some residual functional enzyme are known as CRIM-positive patients.[24] Research has shown that CRIM-positive patients tend to have a positive motor response to GAA gene-replacement therapies while CRIM-negative patients generally do not.[24] Some studies have shown that CRIM-negative patients experienced more clinical decline, required invasive ventilation, and had increased risk of death regardless of ongoing ERT.[24] Severe immune responses during ERT have included hypersensitivity reactions, hypercoagulation, and anaphylaxis.[25-27] CRIM status is determined by Western blot analysis of patient fibroblast cells.[24] Prior to ERT, the patient's CRIM status is ascertained to assess the need for concomitant immune tolerance induction (ITI) therapy to optimize response to ERT and avoid the potential for immune-mediated reactions and poor outcomes.[10,11,13,28] Various protocols have been developed for tolerance induction in CRIM-negative patients. Guidance for ERT initiation and discontinuation has been largely based on expert consensus,

and some experts suggest discontinuing ERT if skeletal muscle function or respiratory function has not stabilized or improved within 2 years of treatment initiation.[29] Considerations for starting and stopping ERT based upon European consensus are listed in **Table 2**.

**Table 2:** Considerations for Starting and Stopping Enzyme Replacement Therapy[29]

| Starting Enzyme Replacement Therapy (ERT) | Stopping Enzyme Replacement Therapy (ERT) |
|---|---|
| Confirmed Pompe disease diagnosis | Severe infusion-associated reactions that cannot be managed properly |
| Symptomatic disease | High antibody titers are detected that significantly counteract the effect of ERT |
| Patient commitment to regular treatment and monitoring | Patient wishes to stop ERT |
| Clinician commitment to regular treatment and monitoring | Patient does not comply with regular infusions or yearly clinical assessments |
| Residual skeletal and respiratory function on which to base assessments of functionally relevant and clinically important maintenance or improvement | No indication that skeletal muscle function and/or respiratory function have stabilized or improved in the first 2 years after start of treatment, based on clinical assessments |
| No co-morbid life-threatening illness in an advanced stage, where treatment to sustain life is inappropriate | Patient has another life-threatening illness that is in an advanced stage, where treatment to sustain life is inappropriate |

Clinically important outcomes for Pompe disease include morbidity, mortality, disease progression, ventilator use, and improvements in motor, pulmonary, or cardiac function. Pulmonary function assessment in Pompe disease patients is often obtained by measurement of FVC and maximal inspiratory and expiratory muscle pressures (MIP and MEP, respectively).[27] Diaphragm weakness is suspected if there is a 10% or greater decrease of FVC in the supine compared with the upright position; a 30% or greater decrease indicates severe weakness.[30] In chronic diseases such as chronic obstructive pulmonary disease (COPD), at least a 15% change over a year has been considered clinically meaningful.[31] The six-minute walk test (6MWT) has been used to measure gross motor function and the functional exercise level for daily physical activities in Pompe disease patients.[25,27] Normal values for the 6MWT in healthy adults are at least 500 meters but can be as high as 700 meters in healthy adolescents.[25,27] The 6MWT has been extensively used to measure response to treatment in patients with chronic disease such as COPD and heart failure.[31] One study found the minimum clinical difference where patients noticed improvement was a mean change of roughly 40 meters from baseline, while patients noticed decline when the test was -70 meters worse than previous measurements.[31] The Pompe Pediatric Evaluation of Disability Index (Pompe-PEDI) is used in children from roughly 6 months to 14 years old and measures mobility, function, and self-care in Pompe disease. [25,27] The Pompe-PEDI is administered as a combination of interview questions and parent reported items scored as “capable” or “uncapable” then converted to a 0-100 continuum.[25,27] The higher the score, the more skills the child can perform.[25,27] The 36-item Short-Form Health Survey (SF-36) is an interview and self-administered questionnaire designed to assess health-related quality of life in healthy and unhealthy adult populations.[32] The complete SF-36 has eight scaled scores; the scores are weighted sums of the questions in each section and range from 0-100 where lower scores indicate more disability. The 12-item Short Form Health Survey (SF-12) is an abbreviated version of the SF-36 which is comprised of a physical component summary (PCS) and mental health component summary (MHC) scale score.[33] The SF-12 uses the same 8 domains found in the SF-36 but only includes one or two items from each of the eight SF-36 scale sections.[33] As with the SF-36, the SF-12 score ranges from 0-100 (high score indicates better physical function).[33] Both the SF-12 and SF-36 have been found to correlate closely with one another.[33] Although the 6MWT, FVC, Pompe PEDI, SF-36, and SF-12 have been utilized to assess progress for many chronic conditions, the significance of these outcomes and their respective minimal clinically important differences have generally not been validated in Pompe disease.[34]

**Methods:**
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

**Systematic Reviews:**
A 2017 Cochrane systematic review assessed the safety, effectiveness, and appropriate dose regimen of enzyme replacement therapy for the treatment of IOPD.[3] Only a single low-quality trial (N=18) was identified which evaluated hospitalized infants (<26 weeks of age at enrollment) with confirmed IOPD.[3] The study compared two different alglucosidase alfa dose regimens (20 mg/kg versus 40 mg/kg) given at 2-week intervals.[3] The alglucosidase alfa treatment results were also compared to an untreated historical control group.[3] Overall, there was low-quality evidence of no difference between the 20 mg/kg and 40 mg/kg treatment groups for outcomes in cardiac function, motor development, and proportion of children free of invasive ventilation at 52 weeks.[3] Quality of evidence was limited due to lack of blinding, unclear random sequence generation and allocation concealment, and poor reporting of study methods as there were little to no numerical results available by dose group.[3] The trial also reported that long-term alglucosidase alfa treatment extended survival as well as ventilation-free survival and improved cardiomyopathy compared to the untreated control group, but the magnitude of benefit could not be quantitatively analyzed, and the quality of evidence was downgraded due to selective reporting.[3] A meta-analysis showed no significant difference for infusion-related events between the high and low-dose alglucosidase alfa treatment groups.[3]

After review, 3 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

**New Guidelines:**
No high-quality guidelines were identified which met quality inclusion criteria.

*Additional Guidelines for Clinical Context*:
A multidisciplinary panel of Canadian physicians released consensus guidelines for healthcare professionals who are involved in the care of patients with Pompe disease.[35] Although it was reported that the level of evidence was examined and graded based on the Oxford Centre for Evidence-Based Medicine and the international GRADE group approach to clinical guidelines, no methodological details were reported.[35] There was no systematic guideline development method described, strength of evidence for guideline recommendations were not provided, and the recommendations were based on expert opinion.[35] In addition, the authors reported several conflicts of interests including providing consultative services to the manufacturer Genzyme as well as receiving research support and consultancy fees.[35] Based these factors, the recommendations from this publication were excluded from this review.

**New Formulations or Indications:**
None

**New FDA Safety Alerts:**
None

**Randomized Controlled Trials:**
A total of 28 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

**NEW DRUG EVALUATION:**

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

**Clinical Efficacy:**
Avalglucosidase alfa (Nexviazyme™) is a recombinant human acid alfa glucosidase approved for use in patients with late-onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency).[1,2] Avalglucosidase is a prodrug of the previously marketed alglucosidase alfa (Lumizyme™) and is administered as an intravenous infusion at a dose of either 20 mg/kg (patients ≥30 kg) or 40 mg/kg (patients <30 kg) once every 2 weeks.[1,2] The FDA approved avalglucosidase alfa in 2021 for the treatment of patients 1 year of age and older with late-onset Pompe disease.[1,2]

Safety and efficacy of avalglucosidase alfa was assessed in one unpublished, phase 3, randomized, double-blind, multinational, multicenter NI trial in ERT-naïve LOPD patients aged 16 years and older (EFC14028 "COMET"- **Table 5**).[1,2] Patients (n=100) were randomly allocated in a 1:1 ratio to either avalglucosidase alfa 20 mg/kg (n=51) or alglucosidase alfa at 20 mg/kg every other week (n=49) for 49 weeks.[1,2] There were differences in a number of baseline characteristics. The avalglucosidase alfa arm had fewer Hispanic or Latino representation, while the alglucosidase alfa arm contained no patients of Asian descent.[1] Baseline mean and median percent predicted FVC and distance walked in the 6MWT were higher in the avalglucosidase alfa arm than in the alglucosidase alfa arm.[1] In addition, there were slightly more patients in the avalglucosidase arm that did not require walking device assistance.[1] Patient ages ranged from 16 to 78 years and the mean and median ages for the two arms was roughly 48 years.[1] Mean disease duration for both arms was about 13 years, but the range was wider in the avalglucosidase arm (0.9 to 58.2 years) compared to alglucosidase (0.4 to 38.2 years).[1] Patients were excluded if they had any prior alglucosidase or ITI therapy, were dependent upon invasive ventilation, were unable to perform repeated percent predicted FVC measurements in upright position of between 30% and 85%, were unable to ambulate 40 meters without stopping and without an assistive device, or had known history of Pompe-specific cardiac hypertrophy.[1] The primary outcome was LSM change in percent predicted FVC in the upright position from baseline to 49 weeks.[1,2] The non-inferiority (NI) margin for the lower bound of the two-sided 95% confidence interval for the difference between the two treatment arms was set at -1.1%.[1] The NI margin of -1.1% was determined using the results of trial AGLU02704 (LOTS), a phase 3, randomized, double-blinded, placebo-controlled, superiority trial of alglucosidase alfa.[1] Clinically relevant secondary endpoints were the estimated treatment difference of distance walked in the 6MWT and health-related quality of life as measured by the SF-12.[1] The

49-week study was followed by an open-label treatment period of up to 144 weeks in which all participants received avalglucosidase alfa regardless of their original randomization group.[1]

Ninety-five of the enrolled 100 patients completed the trial.[1] At 49 weeks, the estimated mean change from baseline in percent predicted FVC was higher in the avalglucosidase alfa arm (2.9%) versus alglucosidase alfa (0.5%) with an estimated treatment difference of 2.4% (95% CI -0.1 to 5.0; p=0.06) in favor of avalglucosidase alfa.[1,2] With the lower bound of the 95% CI for the difference larger than the prespecified NI margin (-1.1%), the trial met noninferiority for the primary efficacy endpoint but did not achieve statistical superiority.[1] The estimated mean change from baseline to week 49 in the 6MWT was higher in the avalglucosidase alfa arm (32.2 meters) versus alglucosidase alfa (2.2 meters) with an estimated treatment difference of 30.0 meters (95% CI 1.3 to 58.7; p=0.04) in favor of avalglucosidase alfa.[1] For the other secondary endpoints including SF-12 PCS and SF-12 MCS scores, there were no statistically significant differences between groups compared to baseline.[1]

The FDA reviewed data from the open-label extension trial where all remaining patients who had received alglucosidase alfa treatment were switched over to avalglucosidase alfa 20 mg/kg to continue treatment every other week until week 97.[1] There were 23/44 patients available for assessment of the primary outcome at the data cutoff point.[1] The mean change in percent predicted FVC from week 49 to week 97 among the 23 patients was -0.1% (95% CI -3.2 to 2.8; p=0.92), which failed to show a statistically significant improvement.[1] There were 26/44 crossover patients available for assessment of the 6MWT during the same time period and the mean change in distance walked in 6MWT from week 49 to 97 among the 26 patients was 8.6 meters (95% CI -20.4 to 37.5; p=0.55), which also failed to show a statistically significant improvement.[1]

A third unpublished, phase 2, open-label, ascending dose trial (ACT14132) was reviewed by the FDA to assess safety of avalglucosidase alfa for use in IOPD patients who experienced clinical decline or were unresponsive to at least 6 months of alglucosidase therapy.[1] Secondary objectives of the study were to determine the effect of avalglucosidase alfa treatment on functional improvements and health-related quality of life as assessed through echocardiography, the Pompe-PEDI, and other measurement tools.[1] Enrolled patients included males and females <18 years of age (mean 6.7 years; range 1 to 12 years) with confirmed GAA enzyme deficiency and cardiomyopathy at time of diagnosis who had been receiving a consistent stable dose of alglucosidase alfa (between 20 mg/kg and 40 mg/kg) for at least 6 months immediately before trial entry. Initially, 11/22 patients were given avalglucosidase alfa at 20 mg/kg (n=6) or 40 mg/kg (n=5) for 6 months.[1] After the highest tolerated dose of avalglucosidase alfa was determined, the remaining 11 patients entered a separate cohort and were randomized 1:1 to be given avalglucosidase alfa 40 mg/kg (n=5) or maintain their stable dose of alglucosidase alfa (n=6) for 6 months.[1] The FDA determined that there was insufficient evidence of avalglucosidase alfa efficacy in the IOPD population due to inadequate sample size and high data variability.[1]

Without evidence of avalglucosidase alfa efficacy in LOPD patients less than 16 years of age, the FDA allowed the manufacturer to conduct a simulation based on pharmacokinetic (PK) data in order to determine whether the 20 mg/kg dose was appropriate across different ages or body weights.[1] It was reported that for the 20 mg/kg dose, patients with lower body weights tended to have lower area under the concentration-time curve over the first two weeks ($AUC_{2w}$) exposure than patients with higher body weight.[1] Therefore, it was argued that pediatric patients with lower body weights likely needed a higher dose to achieve a comparable exposure to adult patients.[1] The FDA also used safety data from study ACT14132 (see **Clinical Safety** section) in patients aged 1 to 11 years with IOPD to consider for approval in pediatric patients with LOPD, as it was determined that patients with IOPD were more severely affected, treatment-experienced, and received higher doses of avalglucosidase alfa over an adequate period of time.[1] Therefore, the incorporation of safety data from IOPD patients along with PK extrapolation based on modeling and simulation was the method employed to select the 40 mg/kg dosing regimen for pediatric patients with LOPD 1 year of age or older weighing <30 kg.

The clinical trials involved small numbers of subjects with mild disease manifestations and did not include patients with severe mobility issues, cardiac hypertrophy, or ventilator dependence. Baseline imbalances in patient characteristics were observed between the 2 groups. Notably, patients in the avalglucosidase group had slightly higher baseline mean/median percent predicted FVC, longer mean/median distance walked in the 6MWT (>20 m) and had (6-7%) less patients who required walking assistance devices than in the alglucosidase alfa arm. Although avalglucosidase alfa met criteria for non-inferiority compared to alglucosidase alfa, it is uncertain whether a 2.4% change in percent predicted FVC is clinically meaningful. It is also unclear why there was only a 0.5% change in percent predicted FVC in the alglucosidase alfa comparator given there was almost a 3% change vs placebo observed in previous trials. Similarly, with avalglucosidase alfa treatment, it is unclear if a 30-meter relative improvement in the 6MWT compared to alglucosidase alfa-treated patients represents a clinically meaningful difference in Pompe disease outcomes. In the Pompe disease (LOTS) trial, it was reported that alglucosidase-treated patients achieved 25 meters on the 6MWT but, in this study, (COMET) it was only 2 meters.[1,25] There was no explanation as to why only about half the patients crossed over to avalglucosidase alfa in the open-label extension trial were available for outcome assessment. With details regarding trial methods absent until the full study is published it is not possible to ascertain to what extent sources of bias such as concealment of allocation and blinding could affect the validity of the results. In addition, high dose avalglucosidase alfa (40 mg/kg) for LOPD patients <30kg was based on a manufacturer-derived model and indirect evidence. The FDA concluded that more long-term data is necessary to determine whether patients treated with avalglucosidase alfa will experience a decline in effectiveness over time similar to alglucosidase alfa or whether initial gains with treatment will persist beyond 2-3 years.[1] With a primary study population of 100 patients dispersed among 69 centers in 26 countries, it is unlikely that adequate oversight and standardized practices could be fully achieved. The small sample size and underrepresentation of minorities further limits the applicability of results to the general Oregon Medicaid population.

**Clinical Safety:**

There were 138 patients in the avalglucosidase alfa combined safety population, 119 who were age 16 or older with LOPD and 19 patients ages 1 to 11 years old with IOPD. Overall, 91% of these patients had treatment emergent adverse events (TEAEs) with nasopharyngitis (30%) identified as the most common. Moderate to severe adverse events (SAEs) were present in 91/138 (66%) of patients 1 of which was associated with a fatal outcome. Four patients (3%) had an adverse event which lead to discontinuation.

In the comparative efficacy trial (EFC14028), at least 1 or more TEAEs were reported by 44 (86%) of the patients treated with avalglucosidase alfa compared to 45 (92%) of the patients treated with alglucosidase alfa.[1] The most common TEAEs in the avalglucosidase alfa group compared to alglucosidase were influenza (18% vs 4%, respectively) and back pain (24% vs. 10%, respectively).[1] Sixteen patients (31%) who received avalglucosidase alfa had IARs compared to 23 (46%) who received alglucosidase alfa.[1] Three of the IARs in avalglucosidase alfa treated patients were categorized as severe reactions.[1] Four patients on avalglucosidase alfa and two on alglucosidase alfa experienced anaphylaxis during the primary analysis period.[1] The most common adverse events that occurred during treatment over 49 weeks in the avalglucosidase and alglucosidase groups, respectively, were headache (22% vs. 33%), fatigue (18% vs. 14%), diarrhea (12% vs. 16%), nausea (12% vs. 14%), arthralgia (10% vs. 16%), dizziness (10% vs. 8%), and myalgia (10% vs. 14%).[1,2] The adverse reactions reported during the Study 1 are summarized in **Table 3**.

**Table 3.** Adverse events occurring in more than 10% of patients treated with avalglucosidase alfa compared to alglucosidase alfa in Study 1 [1,2]

| Adverse reaction | Avalglucosidase alfa (n=51) | Alglucosidase alfa (n=49) |
|---|---|---|
| Headache | 22% | 33% |
| Fatigue | 18% | 14% |
| Diarrhea | 12% | 16% |
| Nausea | 12% | 14% |
| Arthralgia | 10% | 16% |
| Dizziness | 10% | 8% |
| Myalgia | 10% | 14% |

In the ACT14132 study (n=11), all patients in the avalglucosidase alfa and alglucosidase alfa groups reported TEAEs. TEAEs reported in the highest frequency among avalglucosidase alfa compared to alglucosidase groups were cough, device occlusion, diarrhea, eye irritation, headache, tachypnea, pyrexia, rhinorrhea, upper respiratory infection (URI), rash, and vomiting (40% vs 0% for all, respectively). Essentially all TEAEs were observed in the high-dose avalglucosidase alfa (40 mg/kg) group. No SAEs were determined to be related to avalglucosidase alfa therapy and no deaths occurred in the ACT14132 study.

FDA labeling has a BBW for the possibility of life-threatening hypersensitivity reactions including anaphylaxis, infusion-associated reactions and risk of acute cardiorespiratory failure in susceptible patients with avalglucosidase alfa infusions. Increased incidence of hypersensitivity reactions was observed in patients with higher anti-avalglucosidase alfa antibodies (antidrug antibodies, ADA).[2] The warning also cautions that 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.[2] Also, 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 avalglucosidase alfa infusion.[2] Patients with an acute underlying illness at the time of avalglucosidase alfa infusion may be at greater risk for IARs.[2] The FDA labeling suggests more frequent monitoring of vital signs should be performed during infusion in these susceptible patients, and in the event of a severe IAR, therapy should be immediately discontinued and appropriate medical treatment initiated.[2]

Look-alike / Sound-alike Error Risk Potential: No results identified.

**Comparative Endpoints:**

Clinically Meaningful Endpoints:
1) Survival
2) Functional or symptom improvement
3) Quality of life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Mean change in percent predicted FVC

**Table 4.** Pharmacology and Pharmacokinetic Properties[1,2]

| Parameter | |
|---|---|
| Mechanism of Action | Avalglucosidase alfa is an exogenous source of the GAA, which is required for glycogen cleavage. Due to an inherited GAA deficiency or absence, glycogen accumulates in the tissues of patients with Pompe disease. Mannose-6-phosphate on avalglucosidase alfa mediates binding to M6P receptors on the cell surface with high affinity. After binding, it is internalized and transported to lysosomes where it is activated for increased enzymatic glycogen cleavage. |
| Oral Bioavailability | N/A |
| Distribution and Protein Binding | Vd: 3.4 L; Protein binding is unknown |
| Elimination | Not reported |
| Half-Life | 1.6 hours |
| Metabolism | Metabolized into small peptides and amino acids via catabolic pathways |

Abbreviations: GAA=acid alpha-glucosidase; L=liters; N/A=not applicable; Vd=volume of distribution; 6MP=Mannose-6-phosphate.

**Table 5.** Comparative Evidence Table

| Ref./ Study Design | Drug Regimens/ Duration | Patient Population | N | Efficacy Endpoints | ARR/NNT | Safety Outcomes | ARR/NNH | Risk of Bias/ Applicability |
|---|---|---|---|---|---|---|---|---|
| 1. Study 1 (COMET) Phase 3, MC, DB, RCT [1,2] | 1. Avalglucosidase alfa: 20 mg/kg every other week (n=51)<br><br>2. Alglucosidase alfa: 20 mg/kg every other week (n=49) | Demographics:<br>-Mean Age: 48 years (range 16 to 78 yrs)<br>-Male: 52%<br>-Race: White (94%)<br>-FVC % predicted: 63%<br>-Distance 6MWT: 389 meters<br><br>Key Inclusion Criteria:<br>Males and females with confirmed GAA enzyme deficiency from any tissue source and/or two confirmed GAA gene variants<br><br>Key Exclusion Criteria:<br>-Age <3 years. | ITT:<br>1. 51<br>2. 49<br><br>Attrition:<br>1. 0<br>2. 5 | Primary Endpoint:<br>Changes from Baseline to Week 49 in upright FVC % predicted were numerically greater with avalglucosidase alfa-ngpt vs. alglucosidase alfa<br><br>1. 2.89 ± 0.88% (95% CI, 1.13 to 4.65)<br>2. 0.46 ± 0.93% (95% CI, −1.39 to 2.31)<br><br>LSM±SE difference: 2.43% (95% CI, −0.13 to 4.99; p=0.0626)<br><br>Noninferiority margin = −1.1: avalglucosidase alfa-ngpt noninferior to alglucosidase alfa (p=0.0074)<br><br>Secondary Endpoints: | N/A for all | Any TEAE<br>1. 44 (86%)<br>2. 45 (92%)<br><br>Treatment-related TEAE:<br>1. 23 (45%)<br>2. 24 (49%)<br><br>SAEs:<br>1. 8 (16%)<br>2. 12 (25%)<br><br>AE leading to discontinuation of study drug:<br>1. 0<br>2. 4 (8%) | | **Risk of Bias (low/high/unclear)**:<br>FDA approval was based on one unpublished study. Risk of bias cannot be fully assessed.<br><br>**Applicability**:<br>Patient: LOPD in patients over 16 years without prior ERT. Most patients were between 16 to 78 years of age.<br>Intervention: Avalglucosidase alfa at fixed dose intervals<br>Comparator: Alglucosidase alfa<br>Outcomes: % predicted FVC; 6MWT; Physical and mental QoL assessments via SF-12<br>Setting: 69 centers in 26 countries |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | -cardiac hypertrophy<br>-Wheelchair dependence (inability to ambulate 40 meters)<br>-Dependence on invasive ventilation (noninvasive ventilation allowed)<br>-Inability to perform repeated FVC measurements in upright position of ≥30% to ≤85% predicted<br>-Previous treatment with alglucosidase alfa or any investigational therapy for Pompe disease.<br>-Prior or current use of ITI therapy | | 6MWT change from baseline:<br><br>1. 32.21 ± 9.93 m<br>2. 2.19 ± 10.40 m<br><br>LSM±SE difference:<br>30.01 m (95% CI, 1.33 to 58.69); p=0.0405<br><br>SF-12 (PCS and MCS) change from baseline:<br><br>No difference between groups | | | | |
| Abbreviations: 6MWT = six-minute walk test; AE = adverse events CI = confidence interval; DB = double-blind; ERT = enzyme replacement therapy; GAA=enzyme acid alpha-glucosidase; FVC = forced vital capacity; ITI = immune tolerance induction; ITT = intention to treat; LOPD = late-onset Pompe disease; LSM = least squares mean; MHC = mental health component summary; MC = multi-center; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PCS = physical component summary; PP = per protocol; RCT = randomized-controlled trial; TEAE = treatment emergent adverse events; SAE = serious adverse events; SF12 = short form twelve | | | | | | | | |

**References:**


1. FDA Center for Drug Evaluation and Research. Nexviazyme Integrated review. Application number761194. Available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=761194#collapseApproval
2. Nexviazyme (avalglucosidase alfa) Prescribing Information. Genzyme Corp. Cambridge, MA; Aug. 2021.
3. Chen M, Zhang L, Quan S. Enzyme replacement therapy for infantile-onset Pompe disease. *Cochrane Database of Systematic Reviews*. 2017;2017(11).
4. van der Ploeg AT, Reuser AJJ. Pompe's disease. *The Lancet*. 2008;372(9646):1342-1353.
5. Ferreira CR, Gahl WA. Lysosomal storage diseases. *Translational science of rare diseases*. 2017;2(1-2):1-71.
6. Burton BK, Charrow J. Newborn screening for lysosomal storage disorders in Illinois: The initial 15-month experience. *J Pediatr* 2017; 190: 130-135.
7. Hopkins, PV, Klug, T. Incidence of 4 lysosomal storage disorders from 4 years of newborn screening. JAMA Pediatr 2018; 172(7): 696-697.
8. Leslie N, Bailey L. Pompe Disease. 2007 Aug 31 [Updated 2017 May 11]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews®. Seattle (WA): University of Washington, Seattle; 1993-2021.
9. Oregon Health Authority, Public Health Division. Oregon State Public Health Laboratory, Newborn Screening Letter. 9/1/2018 https://www.oregon.gov/oha/PH/LABORATORYSERVICES/NEWBORNSCREENING/Pages/index.aspx Accessed 11/2/2021.
10. American Association of Neuromuscular & Electrodiagnostic Medicine. Diagnostic criteria for late-onset (childhood and adult) Pompe disease. *Muscle Nerve.* 2009;40(1):149-160.
11. Kishnani PS, Steiner RD, Bali D, et al. Pompe disease diagnosis and management guideline [published correction appears in *Genet Med.* 2006 Jun;8(6):382. ACMG Work Group on Management of Pompe Disease [removed]; Case, Laura [corrected to Case, Laura E]]. *Genet Med.* 2006;8(5):267-288.
12. Chan J, Desai AK, Kazi ZB, et al. The emerging phenotype of late-onset Pompe disease: A systematic literature review. *Mol Genet Metab* 2017;120(3):163–172.
13. Cupler EJ, Berger KI, Leshner RT, et al. Consensus treatment recommendations for late-onset Pompe disease. *Muscle Nerve.* 2012;45(3):319-333. doi:10.1002/mus.22329
14. Kroos M, Hoogeveen-Westerveld M, van der Ploeg A, et al. The genotype-phenotype correlation in Pompe disease. *Am J Med Genet C: Semin Med Genet* 2012;160(1):59–68.
15. Shieh JJ, Lin CY. Frequent mutation in Chinese patients with infantile type of GSD II in Taiwan: evidence for a founder effect. *Hum Mutat* 1998;11(4):306–312.
16. Becker JA, Vlach J, Raben N, et al. The African origin of the common mutation in African American patients with glycogenstorage disease type II. *Am J Hum Genet* 1998;62(4):991–994.
17. Esmer C, Becerra-Becerra R, Peña-Zepeda C, Bravo-Oro A. A novel homozygous mutation at the GAA gene in Mexicans with early-onset Pompe disease. *Acta Myol*. 2013;32(2):95-99.
18. Huie ML, Hirschhorn R, Chen AS, et al. Mutation at the catalytic site (M519V) in glycogen storage disease type II (Pompe disease) *Hum Mutat.* 1994;4:291–293.
19. Labrousse P, Chien YH, Pomponio RJ, et al. Genetic heterozygosity and pseudodeficiency in the Pompe disease newborn screening pilot program. *Mol Genet Metab* 2010;99(4):379–383.
20. Kumamoto S, Katafuchi T, Nakamura K, et al High frequency of acid alpha-glucosidase pseudodeficiency complicates newborn screening for glycogen storage disease type II in the Japanese population. *Mol. Genet. Metab.,* 97 (2009), pp. 190-195
21. Lim J-A, Li L, Raben N. Pompe disease: from pathophysiology to therapy and back again. *Front Aging Neurosci.* 2014;6:177-177.

22. Laukkanen JA, Khan H, Kurl S, et al. Left ventricular mass and the risk of sudden cardiac death: a population-based study. *Journal of the American Heart Association.* 2014;3(6):e001285-e001285.
23. Harlaar L, Hogrel J-Y, Perniconi B, et al. Large variation in effects during 10 years of enzyme therapy in adults with Pompe disease. *Neurology*. 2019;93(19):e1756-e1767.
24. Kishnani PS, Goldenberg PC, DeArmey SL, et al. Cross-reactive immunologic material status affects treatment outcomes in Pompe disease infants. *Mol Genet Metab*. 2010;99(1):26-33.
25. FDA Center for Drug Evaluation and Research. Lumizyme Multi-Discipline Review. Application Number 125291Orig1s136. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/125291s000TOC.cfm.
26. Finkleman FD, Madden KB, Morris SC, et al. Anti-cytokine antibodies in carrier proteins. *J Immun.* 1993. 151: 1235-1244.
27. FDA Center for Drug Evaluation and Research. Myozyme Multi-Discipline Review. Application Number 125141s000. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/125141s000_MyozymeTOC.cfm
28. Lumizyme (alglucosidase alfa) Prescribing Information. Genzyme Corp. Cambridge, MA; Feb. 2020.
29. van der Ploeg AT, Kruijshaar ME, Toscano A, et al. European consensus for starting and stopping enzyme replacement therapy in adult patients with Pompe disease: a 10-year experience. *Eur J Neurol.* 2017;24(6):768-e31.
30. ATS/ERS Statement on Respiratory Muscle Testing. *American Journal of Respiratory and Critical Care Medicine*. 2002;166(4):518-624.
31. Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH: Interpreting small differences in functional status: the Six Minute Walk Test in chronic lung disease patients. *Am J Respir Crit Care Med* 1997, 155:1278–1282.
32. Ware JE Jr., Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. *J Clin Epidemiol* 1998;51:903–912.
33. Gandek B, Ware JE, Aaronson NK, et al. Cross-Validation of Item Selection and Scoring for the SF-12 Health Survey in Nine Countries: Results from the IQOLA Project. *Journal of Clinical Epidemiology*. 1998;51(11):1171-1178.
34. Lachmann R, Schoser B. The clinical relevance of outcomes used in late-onset Pompe disease: can we do better? *Orphanet J Rare Dis.* 2013;8:160-160.
35. Tarnopolsky M, Katzberg H, Petrof BJ, et al. Pompe Disease: Diagnosis and Management. Evidence-Based Guidelines from a Canadian Expert Panel. *Can J Neurol Sci.* 2016;43(4):472-485.

**Appendix 1:** Current Preferred Drug List

| Generic | Brand | Form | PDL |
|---|---|---|---|
| alglucosidase alfa | LUMIZYME | VIAL | N |
| avalglucosidase alfa-ngpt | NEXVIAZYME | VIAL | |

**Appendix 2:** Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to November 05, 2021>

1. Pompe disease.mp. or Glycogen Storage Disease Type II/ 2284
2. alglucosidase.mp. / 152
3. avalglucosidase.mp. / 4
4. 2 or 3/ 155
5. 1 and 4/ 141
6. limit 5 to (english language and humans and (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))/ 28

**Appendix 3:** Prescribing Information Highlights

## HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use NEXVIAZYME™ safely and effectively. See full prescribing information for NEXVIAZYME.**

**NEXVIAZYME (avalglucosidase alfa-ngpt) for injection, for intravenous use**
**Initial U.S. Approval: 2021**

**WARNING: SEVERE HYPERSENSITIVITY REACTIONS, INFUSION-ASSOCIATED REACTIONS, and RISK OF ACUTE CARDIORESPIRATORY FAILURE IN SUSCEPTIBLE PATIENTS**

***See full prescribing information for complete boxed warning.***

**Hypersensitivity Reactions Including Anaphylaxis**

- **Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available. If a severe hypersensitivity reaction occurs, NEXVIAZYME should be discontinued immediately and appropriate medical treatment should be initiated. (5.1)**

**Infusion-Associated Reactions (IARs)**

- **If severe IARs occur, consider immediate discontinuation and initiation of appropriate medical treatment. (5.2)**

**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 NEXVIAZYME infusion. (5.3)**

### ----------INDICATIONS AND USAGE----------

NEXVIAZYME is a hydrolytic lysosomal glycogen-specific enzyme indicated for the treatment of patients 1 year of age and older with late-onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency). (1)

### ----------DOSAGE AND ADMINISTRATION----------

- Consider administering antihistamines, antipyretics, and/or corticosteroids prior to NEXVIAZYME administration to reduce the risk of IARs. (2.1)
- Must be reconstituted and diluted prior to use.
- See full prescribing information for administration instructions including the recommended infusion rate schedule. (2.1, 2.3, 2.4)
- NEXVIAZYME is administered as intravenous infusion. For patients weighing (2.1):
  - ≥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.
- See the full prescribing information for dosage modifications due to hypersensitivity reactions or IARs. (2.2)

### ----------DOSAGE FORMS AND STRENGTHS----------

For injection: 100 mg of avalglucosidase alfa-ngpt as a lyophilized powder in a single-dose vial for reconstitution. (3)

### ----------CONTRAINDICATIONS----------

None. (4)

### ----------WARNINGS AND PRECAUTIONS----------

See boxed warning. (5.1, 5.2, 5.3)

### ----------ADVERSE REACTIONS----------

The most common adverse reactions (>5%) were headache, fatigue, diarrhea, nausea, arthralgia, dizziness, myalgia, pruritus, vomiting, dyspnea, erythema, paresthesia and urticaria. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Genzyme at 1-800-745-4447 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

**See 17 for PATIENT COUNSELING INFORMATION.**

**Revised: 8/2021**

# Pompe Disease

**Goal(s):**

- Ensure medically appropriate use of approved agents for the treatment of Pompe disease

**Length of Authorization:**

- Up to 12 months

**Requires PA:**

- Alglucosidase alfa (pharmacy and physician administered claims)
- Avalglucosidase alfa (pharmacy and physician administered claims)

**Covered Alternatives:**

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

**Table 1: FDA-approved Dosage and Administration**

| Agent | Indication | Age Minimum | Dosing Regimen |
|---|---|---|---|
| **Al**glucosidase alfa | Early Onset Pompe Disease (EOPD)<br>Late Onset Pompe Disease (LOPD) | None | 20 mg/kg IV once every 2 weeks |
| **Aval**glucosidase alfa | Late Onset Pompe Disease (LOPD) | ≥ 1 year | < 30 kg: 40 mg/kg IV once every 2 weeks |
| | | | ≥ 30 kg: 20 mg/kg IV once every 2 weeks |

| Approval Criteria | | |
|---|---|---|
| 1. What diagnosis is being treated? | Record ICD10 code. | |
| 2. Is the diagnosis funded by OHP? | **Yes:** Go to #3 | **No:** Pass to RPh. Deny; not funded by the OHP. |

| Approval Criteria | | |
|---|---|---|
| 3. Is the requested agent for an approved indication and dosed appropriately based on age and weight taken within the past month? (**see Table 1**) | **Yes:** Document patient weight and go to #4.<br><br>Weight: _____ | **No:** Pass to RPh. Deny; medical appropriateness. |
| 4. Is there documentation that the patient is switching enzyme replacement therapy (ERT) agents due to lack of benefit with prior therapy? | **Yes:** Pass to RPh. Deny; medical appropriateness | **No:** Go to #5 |
| 5. Is there documentation that the provider has assessed the patient for signs or susceptibility to the following?<br>• Fluid volume overload<br>• Acute underlying respiratory illness<br>• Compromised cardiac or respiratory function necessitating fluid restriction | **Yes:** Go to #6 | **No:** Pass to RPh. Deny; medical appropriateness |
| 6. Is the request for continuation of therapy previously approved by FFS? | **Yes:** Go to **Renewal Criteria** | **No:** Go to #7 |
| 7. Is the treatment for the diagnosis of Pompe disease confirmed by either DNA testing or enzyme assay (e.g. acid alpha-glucosidase activity test)? | **Yes:** Go to #8 | **No:** Pass to RPh. Deny; medical appropriateness |
| 8. Is this request from a metabolic specialist, biochemical geneticist, or has provider documented experience in the treatment of Pompe disease? | **Yes:** Go to #9 | **No:** Pass to RPh. Deny; medical appropriateness |

| Approval Criteria | | |
|---|---|---|
| 9. Is the request for treatment of late-onset Pompe disease (LOPD)? | **Yes:** Go to #13 | **No:** Go to #10 |
| 10. Has the provider documented a baseline value for ALL the following assessments?<br>• Muscle weakness/Motor function? (e.g. AIMS, PDMS-2, Pompe PEDI, etc)<br>• Respiratory status (e.g. FEV, FVC, or other age-appropriate test of pulmonary function)?<br>• Cardiac imaging (e.g. chest x-ray, echocardiography)?<br>• CRIM status? | **Yes:** Document baseline results and go to #11 | **No:** Pass to RPh. Deny; medical appropriateness |
| 11. Is the patient CRIM-negative? | **Yes:** Go to #12 | **No:** Approve for 3 months<br><br>If approved, a referral will be made to case management by the OHA. |
| 12. Is there documentation that concomitant immune tolerance induction (ITI) therapy will be initiated with enzyme replacement therapy (ERT)? | **Yes:** Approve for 3 months | **No:** Pass to RPh. Deny; medical appropriateness |
| 13. Is the patient 5 years of age or older? | **Yes:** Go to #14 | **No:** Go to #15 |
| 14. Is there a baseline documentation for both of the following?<br>• Pulmonary function test (PFT) with spirometry including baseline percent predicted forced vital capacity (FVC)<br>• Demonstration of completed 6-minute walk test (6MWT)<br>-OR-<br>Muscle weakness in the lower extremities? | **Yes:** Approve for 6 months<br><br>Document baseline results.<br><br>If approved, a referral will be made to case management by the OHA. | **No:** Pass to RPh. Deny; medical appropriateness |

| Approval Criteria | | |
|---|---|---|
| 15. Has the provider documented a baseline value for both of the following assessments:<br>• Muscle weakness/Motor function? (e.g. AIMS, PDMS-2, Pompe PEDI, etc)<br>• Respiratory status (e.g. FEV, FVC, or other age-appropriate test of pulmonary function)? | **Yes:** Approve for 3 months<br><br>Document baseline results.<br><br>If approved, a referral will be made to case management by OHA. | **No:** Pass to RPh. Deny; medical appropriateness |

| Renewal Criteria | | |
|---|---|---|
| 1. Is there documented evidence of adherence and tolerance to the approved infusion therapy regimen through claims history and/or provider assessment? | **Yes:** Go to #2 | **No:** Pass to RPh, Deny; medical appropriateness |
| 2. Is this a request for **al**glucosidase alfa? | **Yes:** Go to #3 | **No:** Go to #5 |
| 3. Is this the <u>first</u> renewal for **al**glucosidase alfa? | **Yes:** Go to #4 | **No:** Go to #5 |
| 4. Is there documentation that the patient has recently been tested* for IgG antibody formation?<br>** Patients should be monitored for IgG antibody formation every 3 months for 2 years and then annually thereafter per manufacturer labeling.* | **Yes**: Go to #5 | **No:** Pass to RPh. Deny; medical appropriateness |
| 5. Compared to baseline measurements, is there documented evidence of improvement or stabilization in muscle, motor, and/or respiratory function? | **Yes:** Go to #6 | **No:** Pass to RPh. Deny; medical appropriateness |
| 6. Is patient under 5 years old? | **Yes:** Approve for 3 months | **No:** Go to #7 |

| Renewal Criteria | | |
|---|---|---|
| 7. Has the patient received the requested therapy for at least 6 months? | **Yes:** Approve for 12 months | **No:** Approve for 3 months |

*P&T/DUR Review: 2/22 (DE); 4/21 (DE)*
*Implementation: 4/1/22; 5/1/21*