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New Drug Evaluation: alglucosidase alfa, intravenous

Date of Review: April 2021
Generic Name: alglucosidase alfa

End Date of Literature Search: 12/31/2020
Brand Name (Manufacturer): Lumizyme™
Dossier Received: no

Research Questions:

1. What is the efficacy and effectiveness of alglucosidase alfa in reducing symptoms, improving functional outcomes, and improving mortality in patients with Pompe disease?
2. What are the harms of alglucosidase 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?

Conclusions:

- There is insufficient evidence from one randomized, placebo-controlled trial in late-onset Pompe disease (LOPD) patients that treatment with alglucosidase alfa over 78 weeks resulted in a statistically significant improvement from baseline in the 6-minute walk test (6MWT) and percent predicted forced vital capacity (FVC) compared to placebo ([Mean difference 28.1 m [95% CI, 2.1 to 54.2]; p=0.03) and (Mean difference 3.4% (95% CI, 1.0 to 5.8); p=0.006), respectively].[1-4] The clinical significance of a 28 m improvement in the 6MWT and a 3-point percentage change in % FVC in this patient population is unclear.
- There is low quality evidence from one small randomized open-label trial in patients with infantile-onset Pompe disease (IOPD) that treatment with alglucosidase alfa over 52 weeks resulted in increased proportion patients alive without need for ventilatory support (15/18 patients [83%]) compared to untreated historical controls (1/61 patients [2%]).[5,6] There were also 15/18 treated patients who showed reductions in left ventricular mass index (LVMI) [mean decrease 118 g/m^2 (range 45 to 193 g/m^2)], but the clinical significance of this change for individual patients with Pompe disease is unclear. [5,6]
- There is low quality evidence from one small non-randomized open-label trial that treatment with alglucosidase alfa over 2 years resulted in an increased proportion of patients alive at the end of treatment compared to historical controls [71% (95% CI, 52 to 91%) vs 26% (95% CI, 7 to 46%), respectively].[7]
- Alglucosidase alfa manufacturer label contains a black box warning about increased risk of anaphylaxis, hypersensitivity and immune-related reactions, as well as cardiorespiratory failure. Common adverse effects with alglucosidase alfa treatment ($\geq$ 5%) included rash, pyrexia, urticaria, flushing, and hypertension. [2]
- There is insufficient evidence regarding long-term safety and efficacy for the use of alglucosidase alfa in the treatment of Pompe disease. Evidence is limited by the small population of patients which have received alglucosidase alfa.

Recommendations:

- Add alglucosidase alfa to the PDL class for lysosomal storage disorders.

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- Designate alglucosidase alfa as non-preferred.
- Implement prior authorization (PA) criteria for alglucosidase alfa to ensure medically appropriate use.

Background:
Pompe disease, also known as glycogenosis type II or acid maltase deficiency, is an inherited, autosomal recessive lysosomal storage disease caused by mutations in the alpha-glucosidase gene which leads to a deficiency in the enzyme alpha glucosidase (GAA).[8,9] GAA mutations lead to a nonfunctional GAA enzyme and accumulation of glycogen stored in skeletal and cardiac muscle as well as other tissues.[8,9] 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.[8,9] Generally, early deficiencies in GAA activity result in rapid progression of disease and decline of motor function.[8,9] Although it is most common for Pompe disease to present within the first 2 months of life, it can also manifest at any age after infancy.[8,9] Early-onset Pompe disease with symptoms of cardiomyopathy, if left untreated, typically results in death from cardiorespiratory failure by the second year of life.[8,9]

Pompe disease prevalence differs greatly based on clinical variant, ethnic background and geography, and is estimated to affect roughly 1:40,000 people in the United States. In those with European descent, IOPD is rarer than LOPD with a prevalence of 1:100,000 compared to 1:60,000, respectively.[10] Pompe disease may affect African Americans at a rate as high as 1:14,000.[10] A study of Pompe disease in British Columbia, Canada revealed an incidence of 1 per 115,091 live births.[11] Some of the likely risk factors for development of Pompe disease include a family history of glycogen storage disease (Type 2) where at conception, siblings of a patient have a 25% chance of disease development.[10] A claims-based review from January through December 2020 revealed 14 patients in the Oregon Health Plan (OHP) population with a Pompe disease diagnosis, 3 of whom were Fee-for-Service (FFS) members. Since 2015, there have been 5 patients with FFS claims for alglucosidase alfa. Pompe disease is a funded condition on line 147 (glycogenosis) of the Health Evidence Review Commission (HERC) prioritized list of health services. Newborn screening (NBS) for Pompe disease is not currently mandatory in Oregon.

Pompe disease has been classified into two main phenotypes based on the age of onset, type of organs involved, progression rate, and severity.[12,13] Infantile-onset Pompe Disease (IOPD) often presents before 12 months of age (median age ~4 months), with rapid progression of symptoms such as muscle weakness, feeding issues, underdevelopment, and respiratory distress.[12] Most patients die within this stage without achievement of motor milestones such as turning over, sitting, or crawling.[12,13] Late-onset Pompe disease (LOPD) describes individuals who generally present after 12 months and without cardiac involvement.[12,13] 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.[12,13] Respiratory dysfunction from intercostal and accessory muscle decline is common and may eventually lead to failure.[8,9] In LOPD, male gender and an earlier age of onset may predict a more rapid disease course.[12,13] 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.[12,13]

Table 1: General Characteristics of IOPD versus LOPD[12,13]

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
GAA enzyme activity <1% normal (Complete deficiency)	GAA 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 gene for GAA is located on chromosome 17 and hundreds of variations have been identified.[10,14] 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.[10,14] 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.[12,13] 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.[12,13]

There is evidence to suggest that the presence of cross-reactive immunological material (CRIM) may affect the prognosis of patients with IOPD.[15] By definition, GAA-deficient IOPD patients with at least some residual functional or non-functional enzyme are known as CRIM-positive patients while those with two GAA mutations and unable to synthesize the enzyme are called CRIM-negative.[15] Patients with late-onset Pompe disease are CRIM-positive because they have some residual GAA protein.[15] CRIM status is determined by Western blot analysis of patient fibroblast cells.[15] 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.[15] Along with clinical decline, high anti-rhGAA IgG antibody titers have been noted in many CRIM-negative patients whereas titers in CRIM-positive patients were low.[15] Patients who develop IgE antibodies to ERT may be at a higher risk for developing anaphylaxis and hypersensitivity reactions.[1,16,21] More research is needed to gain improved understanding of CRIM status as a predictive factor of clinical outcomes in Pompe disease.

Treatment for Pompe disease may include a variety of strategies which depend upon patient age, stage, genetic factors, and clinical manifestations.[12-14,17] Management usually requires a multidisciplinary approach with expertise in cardiology, pulmonology, metabolic disease, neurology, rehabilitation services, and nutrition support.[12-14] Respiratory, motor, and nutritional assessments are needed at regular intervals to track disease activity and monitor progress.[12-14] Some studies suggest that enhanced nutrition and exercise may help slow muscle function decline in LOPD patients.[12-14] A cardiology evaluation with echocardiography may be of value to monitor complications such as left ventricular mass index (LMVI) and risk of sudden cardiac death.[12-14,18] Respiratory surveillance is accomplished through regular chest X-rays and pulmonary function tests (PFTs) to ensure airway integrity.[12-14] For those patients with a need for respiratory support, supplemental oxygen or non-invasive ventilatory support may be warranted. Periodic assessment of musculoskeletal function via scoliosis tests and bone mineral density scans are also suggested.[12-14] 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.[12-14] Enzyme replacement therapy (ERT) is typically started upon IOPD diagnosis or once symptomatic Pompe disease is recognized, although goals and expectations may differ between IOPD and LOPD.[12-14] The patient's

CRIM status is ascertained at the start of ERT therapy to assess the need for concomitant immune tolerance induction (ITI) therapy to optimize treatment and avoid the potential for immune-mediated reactions and poor outcomes. [2,12-14] ERT has been studied for many clinical outcomes in Pompe disease including mortality, respiratory function, ventilator dependence, and walking distance, but its effectiveness has shown mixed results.[19] 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.[20]

Table 2: Considerations for Starting and Stopping ERT[20]

Starting ERT	Stopping 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. In clinical studies, the 6MWT has been used to measure gross motor function and the functional exercise level for daily physical activities in Pompe disease patients. Normal values for the 6MWT in healthy adults are at least 500 meters but can be as high as 700 meters in healthy adolescents.[1,21] The 6MWT has been extensively used to measure response to treatment in patients with chronic disease such as chronic obstructive pulmonary disease (COPD) and heart failure.[22] 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.[22] For younger Pompe disease patients and notably in IOPD, the Alberta Infant Motor Scale (AIMS) has been employed to assess infant motor performance over time.[23] The AIMS is a standardized instrument that consists of 58 test items of 1 point each administered in 4 different positions with higher scores representative of more mature motor development.[23] The Peabody Developmental Motor Scale (PDMS-2) is a test of fine and gross motor abilities in areas such as reflexes, stationary, locomotion, object manipulation, grasping, and visual motor integration.[1,21] The PDMS-2 is used in children from birth through 83 months.[1,21] PDMS-2 raw scores are converted to a standardized 100 points where children with scores <80 are classified to be at risk. [1,21] The Pompe PEDI is used in children from roughly 6 months to 14 years old and measures mobility, function, and self-care in Pompe disease. [1,21] 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. [1,21] The higher the score, the more skills the child can perform. [1,21] The Short-Form Health Survey (SF-36) Physical Component score is an interview and self-administered questionnaire designed to assess health-related quality of life in healthy and unhealthy adult populations.[24] 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.[24] Pulmonary function assessment in Pompe disease patients is often obtained by measurement of forced vital capacity (FVC) and maximal inspiratory and expiratory muscle pressures (MIP and MEP, respectively).[21] Diaphragm weakness is suspected if there is a $\geq$10% decrease of FVC in the supine compared with the upright position; a $\geq$30% decrease indicates severe weakness.[25] In chronic diseases such as COPD, at least a 15% change over a year has been considered clinically meaningful.[22] Although the clinical relevance of the 6MWT, FVC, AIMS, PDMS-2, Pompe PEDI, and SF-36

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.[26]
See **Appendix 1** 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:
Alglucosidase alfa (Myozyme™, Lumizyme™) is a hydrolytic lysosomal glycogen-specific enzyme approved for use in patients with Pompe disease (acid alfa-glucosidase [GAA] deficiency).[1,2,21] Alglucosidase alfa is administered as an intravenous infusion at a dose of 20 mg/kg once every 2 weeks. [1,2,21] The FDA approved alglucosidase alfa under the name Myozyme™ in 2006 for the treatment of IOPD in infants and children up to 18 years old.[21] In 2010, FDA approved a second alglucosidase alfa product (Lumizyme™) to treat patients with late onset (non-infantile) Pompe disease at least 8 years of age or older without evidence of cardiac hypertrophy. [1,2,21] At the time, both GAA products were made from different processes and had not been analytically compared. A Risk Evaluation Mitigation Strategy (REMS) program was required for Lumizyme™ to ensure appropriate use according to age limitations and to monitor known risks of anaphylaxis and severe allergic reactions. [1,2,21] In 2014, the FDA reviewed a supplemental BLA for Lumizyme™ with manufacturer-supplied data from an immunogenicity study within the National Taiwan University Hospital (NTUH) newborn screening program.[1,2] The FDA found no evidence of a different antibody response in Lumizyme™ compared to Myozyme™.[1] Since the quality product critical attributes of both products were considered comparable, Lumizyme™ was granted expanded approval to treat all forms of Pompe disease based on safety and efficacy data of Myozyme™ and the REMS requirement was removed.[1,2] Currently, Lumizyme™ is the only formulation available for use in the United States.

Alglucosidase alfa (Lumizyme™) in the treatment of Pompe disease was assessed in one pivotal randomized, double-blind placebo-controlled trial in LOPD patients and in two open-label, historically controlled, multicenter clinical trials in IOPD patients (**Table 5**).

The Late Onset Treatment Study (LOTS) assessed the safety and efficacy of alglucosidase alfa in a randomized, placebo-controlled, 78-week trial in 90 LOPD patients.[1-3] Patients were randomly allocated in a 2:1 ratio to either alglucosidase alfa 20 mg/kg (n=60) or placebo (n=30).[1,3] Baseline characteristics were generally similar, however the alglucosidase alfa group had slightly more men, were older, and generally required less walking device assistance.[1,3] In addition, age of disease symptom onset was different between groups for the alglucosidase alfa versus placebo groups (30 vs. 24 years old, respectively).[1,3] Patients were generally ambulatory; however, almost half required a walking device, and roughly one-third required some type of ventilator support. [1,3] Mean age at first infusion was roughly 43 years old although ages ranged between 10 and 70 years old. [1,3] Patients were excluded if they required invasive ventilator support (as defined by use of an endotracheal tube), or requirements for noninvasive ventilatory support while awake and in an upright position. [1,3] The primary outcomes were distance walked in the 6-minute walk test and percentage of predicted forced vital capacity (FVC). [1,3] Relevant clinical secondary outcomes included percent of predicted quantitative muscle strength testing, percent of predicted maximum inspiratory and expiratory pressure, and Short-Form Health Survey (SF-36) Physical Component score change from baseline. [1,3]

There were 81 of 90 patients who completed the trial. [1,3] At 78 weeks, a statistically significant difference from the baseline 6MWT was observed in the alglucosidase alfa group compared to placebo (+25.1 m vs. -3.0 m, respectively; Mean difference 28.1 m [95% CI, 2.1 to 54.2]; p=0.03). [1,3] There was also a statistically significant change observed from baseline in percent predicted FVC compared to placebo (+1.2 versus -2.2, respectively; Mean difference 3.4% [95% CI, 1.0 to 5.8]; p=0.006). [1,3] No statistically significant changes were observed in the clinically relevant secondary outcomes except for percent predicted maximum expiratory pressure, which reported a slight increase in favor of alglucosidase alfa versus placebo (mean difference 3.8 [95% CI, 0.3 to 7.3]; p=0.04).[1,3]

There was no statistically significant difference in quantitative muscle testing, maximum inspiratory pressure, or SF-36 Physical Component scores. [1,3] A follow-up LOTS extension study lasted 26 additional weeks and yielded similar results for alglucosidase-treated individuals. [1,4] However, when patients in the placebo arm of LOTS were switched to alglucosidase alfa in LOTS Extension, the 6MWT and FVC showed no further deterioration but did not show improvement after 6 months of active treatment. [1,4]

In an open label, phase 2/3 study by Kishnani et. al (AGLU01602), alglucosidase alfa efficacy was assessed in 18 patients (11 males, 7 females) aged 6 months or less (mean 4.6 months) for the treatment of infantile-onset Pompe disease.[1,5,21] Patients were randomized 1:1 and given alglucosidase alfa at either a 20 mg/kg or 40 mg/kg IV infusion once every 2 weeks for 52 weeks. [1,5,21] Doses were adjusted every 4 weeks if needed to account for body weight changes. [1,5,21] The primary endpoint was the proportion of patients alive with no need for invasive ventilation support at 18 months of age compared to survival rates of the age-matched historical control group. [1,5,21] Invasive ventilator-free survival was defined as 1) patient was ventilator free for a 14-day period encompassing the target time point or 2) if the investigator determined that ventilator use was due to a secondary cause at the target time and then the patient was to be followed for 30 more days.[21] If during the follow up period the patient became ventilator-free for 14 consecutive days, the patient was considered ventilator-free.[21] Invasive ventilation was defined as requiring passive ventilation through an endotracheal tube or tracheostomy. [1,5,21] At 52 weeks, 15/18 (83%) patients treated with alglucosidase alfa were alive without need for ventilatory support at 18 months compared to 1 of 65 patients (2%) in the historical cohort. [1,5,21] Although the investigators reported no significant difference between the low-dose and high-dose groups, no data was reported for comparison between doses. For secondary outcomes, there were notable improvements in LVMI [mean decrease 118 g/m^2 (range 45 to 193 g/m^2; n=15)] and 13/18 (83%) of patients demonstrated motor improvements on the AIMS and/or Pompe PEDI score compared to baseline. [1,5,21] With treatment beyond 52 weeks, it was noted, however, that 4 patients required ventilator support and 2 of them died, 1 at 14 months and the other at 25 months.[1,5,21] The extension phase of the study (AGLU02403) was up to 3 years which included 16 surviving patients from the original 18.[1,6,21] The study was identical to AGLU01602 but without randomization. [1,6,21] Of the 16 enrolled patients, 13 completed the study, 2 patients died while in study participation, 1 patient withdrew from the study then died after withdrawal, while one additional patient died after study completion. [1,6,21]

In an open-label, non-randomized study by Nicolino et. al (AGLU01702), the efficacy and safety of alglucosidase alfa was examined in 21 patients with IOPD.[1,7,21] Patients received alglucosidase alfa 20 mg/kg every other week or an escalated dose of 40 mg/kg for up to 168 weeks (median 120 weeks).[1,7,21] The trial included 18 CRIM-positive and 3 CRIM-negative patients between the ages of 3 to 3.5 months at the time of first infusion. [1,7,21] There were 5 patients on invasive ventilatory support at the first infusion. [1,7,21] The primary outcome was the proportion of patients alive at the end of treatment. [1,7,21] Only the results of the primary analysis were compared to an untreated reference cohort of 168 IOPD patient cases. [1,7,21] At the end of 52 weeks, the proportion of patients alive at the end of treatment was higher in the alglucosidase alfa-treated group compared to historical control reference group [71% (95% CI, 52 to 91%) vs 26% (95% CI, 7 to 46%), respectively].[7,21] Of the 16 patients free of invasive ventilatory support at baseline, 44% (7/16) remained free of invasive ventilation, 4 had become ventilator dependent, and 5 patients had died. [1,7,21] These outcomes were not compared to the untreated reference cohort.[1,7,21] A Kaplan Meier method was used to calculate survival estimates at both 52 weeks and 104 weeks for treated patients compared to the untreated historical reference cohort. [1,7,21] Select secondary outcomes of functional assessments were inconsistently reported and could not be compared to historical control due to limited availability of detailed data regarding clinical outcomes. [1,7,21]

It is unclear whether a 28-meter improvement in the 6MWT and a 3-point percentage change in the % FVC after 78 weeks of alglucosidase alfa treatment is a clinically meaningful difference in Pompe disease patients. Since the 6MWT allows patients to rest when desired, it may not be the optimal measurement of maximum exercise capacity in treatment outcomes for Pompe Disease. In the LOTS study, patients in the alglucosidase alfa group were older than the placebo group, and the placebo group also had more walking device use. Given the progressive nature of Pompe disease, this may indicate groups were not comparable

and could have biased results in favor of treatment. For measures of cardiac function, there are no correlations between changes in LVMI and clinical improvements in meaningful outcomes for patients treated with alglucosidase alfa compared to historical controls. Although many patients were reported to have clinically meaningful gains in motor development per the AIMS and Pompe PEDI assessments with alglucosidase alfa treatment, the FDA noted that these patients remained significantly delayed compared to normal age-matched peers, so longer-term follow-up is needed.[1,21] The relatively small number of patients studied in these trials present many challenges to interpretation of the data. In the IOPD studies, only 7 of the 39 patients were CRIM negative so efficacy in this population is unclear. Differences in time from diagnosis, disease severity, and patient ages were not described in detail for all trials which made it difficult to determine what patient populations might respond better (or worse) to ERT. In addition, without details of the patient selection process it is unclear if a historical control group would be an accurate or appropriate comparator. It was unknown if historical controls were appropriately matched based on major prognostic factors such as baseline respiratory and motor function. There may have been changes in standards of care over time such as more access to ventilation access to mobility assistive devices, physical therapy among other important advances among the historical control population. There were no standardized tools used in the trials to measure patient quality of life (QOL), and the available data indicates little to no improvement in QOL, so outcomes in these areas remain mostly unknown. For many of the trials, raw measurements were not reported and there was no comparator group, so assessment of the benefit magnitude and effectiveness of therapy were not possible. More trials with larger numbers of patients are needed to evaluate whether treatment with alglucosidase alfa provides long-term survival benefit, sustained stabilization or improvement of muscle, motor and/or respiratory function, or quality of life improvements in Pompe disease patients.

Clinical Safety:

Safety for the use of alglucosidase alfa in the treatment of IOPD patients is based on over 3 years of clinical trial data in 39 patients.[1,2] Most adverse events occurred either during or within 2 hours of administration. [1,2] Common infusion reactions included rash, pyrexia, urticaria, flushing, and hypertension. In studies with LOPD patients (N=90) treated with alglucosidase alfa, adverse effects were reported compared to placebo. [1,2] Common adverse reactions in at least 5% of alglucosidase-treated patients and at a greater frequency than placebo-treated patients are listed in **Table 3**. [1,2] Hyperhidrosis, fatigue, myalgia, and nausea were reported by patients within 2-48 hours after completion of the alglucosidase alfa infusion. [1,2]

Table 3 Adverse Events in at least 5% of Patients treated with Alglucosidase Alfa in Clinical Trials[1,2]

IOPD Patients	(n=39)		**LOPD Patients**	Alglucosidase alfa (n=60)	Placebo (n=30)
Adverse Events	**N (%)**		**Adverse Events**	**N (%)**	**N (%)**
Rash	7 (18)		Hyperhidrosis	5 (8)	0 (0)
Pyrexia	6 (15)		Urticaria*	5 (8)	0 (0)
Urticaria*	5 (13)		Anaphylaxis	4 (7)	0 (0)
Flushing*	5 (13)		Chest discomfort	4 (7)	1 (3)
Increased blood pressure*	4 (10)		Muscle twitching	4 (7)	1 (3)
Decreased Oxygen Saturation	3 (8)		Myalgia	3 (5)	1 (3)
Cough	3 (8)		Flushing*	3 (5)	0 (0)
Tachypnea	3 (8)		Increased blood pressure*	3 (5)	0 (0)
Tachycardia	3 (8)				
Erythema	2 (5)				

Vomiting	2 (5)				
Rigors	2 (5)				
Pallor	2 (5)				
Cyanosis	2 (5)				
Agitation	2 (5)				
Tremor	2 (5)				

(* = Common adverse events reported in both trials)

FDA labeling has a black boxed warning (BBW) for the possibility of life-threatening anaphylactic reactions, severe allergic reactions and immune mediated reactions with alglucosidase alfa infusions. [1,2] Immune-mediated reactions presenting as proteinuria, nephrotic syndrome, and necrotizing skin lesions have occurred in some patients following alglucosidase alfa treatment. [1,2] Prescribers should provide close patient observation during and after alglucosidase alfa administration and be prepared for appropriate medical management of hypersensitivity and anaphylaxis. [1,2] The majority of patients developed IgG antibodies to alglucosidase alfa within 3 months of treatment. [1,2] Evidence from studies suggest that patients with high and prolonged IgG antibody titers may experience reduced clinical response such as loss of motor function, ventilator dependence, or possibly death. [1,2] The manufacture has suggested patients be monitored for IgG antibody formation every 3 months for 2 years and then annually.[1,2] There is also a BBW for IOPD patients with compromised cardiac or respiratory function in that they may be at risk of serious acute exacerbation of their cardiac or respiratory compromise due to fluid overload and require additional monitoring.[1,2]

Look-alike / Sound-alike Error Risk Potential: Lumizyme™ may be confused with Lumigan™ (bimatoprost) or Lumason™ (Sulfur Hexafluoride Lipid-Type A Microspheres)

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) 6MWT
2) FVC
3) Survival
4) Invasive ventilator support

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

Parameter	
Mechanism of Action	Recombinant, exogenous source of acid alpha-glucosidase (GAA) that binds to lysosomes and is internalized, resulting in increased enzymatic activity in cleaving glycogen
Oral Bioavailability	N/A – administered intravenously
Distribution and Protein Binding	Vd: Infants 1 to 7 months: 96 ± 16 mL/kg
Elimination	N/A
Half-Life	2.3 hours (infants 1-7 months); 2.4 hours (adults)
Metabolism	Unknown – not studied

Abbreviations: hr = hours; kg = kilogram; L = liters; Vd = volume of distribution

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. van der Ploeg T, et al.[1,3] Phase 3 MC, DB, PC N=90	1. alglucosidase alfa 20 mg/kg IV every 2 weeks x 78 weeks (n=60) 2. Placebo IV every 2 weeks x 78 weeks (n=30)	Demographics: -Mean age: 45 years (range 16-70 years) -Male/Female: 1. 57%/43% 2. 37%/63% -Race: White (93%) -Mean disease duration: 9.5 years -Baseline 6MWT 1. 332.2 m 2. 317.9 m -Baseline mean % predicted FVC 1. 55.4% 2. 53.0% -Use of walking device 1. 38% 2. 53% -Use of ventilatory support 1. 33% 2. 37% Key Inclusion Criteria: -confirmed Pompe's disease Dx (GAA deficiency and 2 GAA gene mutations) -≥8 years or older -able to walk 40 m on 6MWT (assistive devices permitted) -% predicted FVC 30% - 80% in upright position, with postural drop in FVC (in L) of ≥10% -muscle weakness in lower extremities (bilateral knee extension > 80% predicted per QMT Key Exclusion Criteria: -any invasive ventilation -noninvasive ventilation while awake and upright -any previous GAA enzyme replacement -major condition that interfered with study compliance or monitoring	ITT: 1. 60 2. 30 Attrition: 1. 5 (8.3%) 2. 4 (13.3%)	Primary Endpoint: 6MWT distance change from baseline 1: +25 m 2: -3 m Mean difference 28.1 m [95% CI, 2.1 to 54.2]; p=0.03) Percent predicted FVC in the upright position 1. 1.2% 2. -2.2% Mean difference 3.4% (95% CI, 1.3 to 5.5) p-value = 0.006 Secondary Endpoint: % predicted maximum expiratory pressure 1. 3.2 2. -0.6 Mean difference 3.8 (95% CI, 0.2 to 7.3) P=0.04	NA for all	Outcome: TEAEs 1. 32 (53.3%) 2. 17 (56.7%) SAEs 1. 13 (22%) 2. 6 (20%) Most common AEs -hyperhidrosis 8% -urticaria 8% -anaphylaxis 7% -chest discomfort 7% -muscle twitching 7% Statistical significance not reported	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (High) IVRS with central computer used but details of randomization and allocation concealment not described; older age of disease onset in treatment group and imbalances in use of walking devices may indicate placebo group has more progressive or severe disease; more males in treatment group Performance Bias: (Unclear) Investigators, patients blinded; Unknown if patient care received was standardized; Manufacturer's Clinical Pharmacy Research Services not blinded Detection Bias: (High) Blinding of outcome assessors not described; independent statistical center and the Data Safety Monitoring Board were unblinded to treatment assignment during interim analysis and review Attrition Bias: (Low) Overall attrition low; sensitivity analysis performed; LOCF and regression model approach was used to create multiple imputations for missing data; worst rank analysis also used Reporting Bias: (Low) All results reported Other Bias: (High) Manufacturer funded the study and its employees involved in preparation and review of the paper **Applicability**: Patient: All LOPD patients; ambulatory; naive to ERT; patients with major condition that interfered with study compliance or monitoring were excluded; lack of ethnic minority inclusion as Pompe may be more common in African American patients Intervention: Alglucosidase alfa 20 mg/kg IV biweekly Comparator: Placebo Outcomes: Primary outcome (% predicted FVC) is a surrogate endpoint; long-term impact on survival, muscle, motor, and respiratory development unknown. Setting: Multinational (Netherlands, France, U.S.)

2. Kishnani PS, et al.[1,5,21] Phase 2/3 (Plus 52-week follow up extension study) MC, OL, randomized N=18	1. alglucosidase alfa 20 mg/kg every 2 weeks x 52 weeks 2. alglucosidase alfa 40 mg/kg every 2 weeks X 52 weeks Untreated historical control (N=61)	Demographics: -Gender: Male 61% -Race: White 39% Black 22% Asian 17% Hispanic 11% -Mean age at first symptoms: 1.6 mo. -Mean age at diagnosis: 3.7 mo. -Mean age at first infusion: 4.6 mo. Key Inclusion Criteria: - documented symptoms of IOPD - skin fibroblast GAA activity <1% of normal mean -hypertrophic cardiomyopathy (LVMI 65g/m^2 by echocardiogram) - age <26 weeks at enrollment Key Exclusion Criteria: -Respiratory insufficiency (O_2 saturation ≤90% or CO_2 partial pressure 55 mmHg (venous) or 40 mmHg (arterial) in room air or any ventilator use -Major congenital anomaly or clinically significant intercurrent illness unrelated to Pompe disease -Any prior alglucosidase alfa treatment	ITT: 1. 9 2. 9 Attrition: 1. 1 2. 0	Primary Endpoint: Survival without ventilatory support at 52 weeks -Treated combined: 15/18 (83%) -Untreated historical control: 1/61 (2%) Secondary Endpoints: Motor Development improvements in AIMS and/or Pompe PEDI: 13/18 (72%) (no scoring details reported) Cardiomyopathy, Change in LVMI: -mean decrease 118 g/m^2 (range 45 to 193 g/m^2) N=15	NA for all	Outcome: Development Anti-rhGAA IgG antibodies -16/18 (89%) Severe AEs -15/18 (83%) IARs -11/18 (61%) Discontinuations due to IARs or AEs -none Deaths 2/18 (11%) -during follow-up period Statistical significance not reported	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Unclear) No details of randomization strategy; open-label potential exclusion of sickest patients (e.g., severely respiratory compromised) could overestimate survival of treatment group. Historical control group selected based on age at first symptoms, age at diagnosis, and other screening criteria for the clinical trial (process not detailed). Treatment and historical controls with similar demographic profiles. Performance Bias: (High) No blinding of clinicians or participants. Timing of infusion was unknown. Detection Bias: (Low) Outcome assessments of echocardiogram and muscle biopsies centrally reviewed by blinded pediatric cardiologist and pathologist. Centralized scoring of motor and cognitive evaluations by non-blinded clinician Attrition Bias: (Low) 1 death in 20 mg/kg group before 52 weeks Reporting Bias: (Unclear) Blood chemistry safety data not reported. No data regarding outcome comparisons between different treatment doses. All other outcomes reported. Other Bias: (High) Primary authors received grant support from Genzyme and were members of disease advisory board for Genzyme. **Applicability**: Patient: IOPD patients age <26 weeks at enrollment Intervention: alglucosidase alfa 20 mg/kg/2 weeks and 40 mg/kg/2 weeks Comparator: Historical control Outcomes: Survival and ventilator use Setting: Multinational USA – 6 centers Europe – 5 centers Taiwan – 1 center Israel – 1 center

3. Nicolino et al. [1,7,21] Phase1/ Phase2 Single arm, OL, Non-randomized N=21	alglucosidase alfa 20 mg/kg IV up to 40 mg/kg every 2 weeks x 52 weeks plus 52-week follow-up Untreated historical control group (N=168)	Demographics: Age range: 3-43 months (median 13 months) Male: 48% Race -White: 71% -Asian: 14% -Black: 10% Median Age at first symptoms: 3 months Median Age at diagnosis: 6.8 months Invasive ventilator support at baseline: 5 (24%) Noninvasive ventilator support (baseline): 2 (10%) LVMI: 193.8 g/m^2 Key Inclusion Criteria: - Pompe disease symptoms by 12 months of age -Skin fibroblast GAA activity ≤2% of normal mean -Age 6–36 months at enrollment -Abnormal left ventricular mass indices (LVMIs) defined as ≥65 g/m^2 for patients up to 12 months old or >79 g/m^2 for patients older than 12 months Key Exclusion Criteria: -Clinical signs or symptoms of cardiac failure with ejection fraction <40% -Major congenital anomaly -Intercurrent organic disease (metabolic disorders) -Prior treatment with ERT	ITT: 21 Attrition: 0	Primary Endpoint: 2-year survival estimate: -Treatment: 71% (95%CI, 52 to 91) -Untreated historical Control : 26% (95% CI, 7 to 46) Secondary Endpoints Unable to compare treated patient outcomes to historical reference cohort. Raw data were not available. Should not be used to establish efficacy. Respiratory function: -Free of ventilator dependency: 44%	NA for all	Outcome: Antibody development 19/20 (95%) SAEs 18/21 (86%) -pneumonia: 8(38%) -respiratory distress: 6 (29%) -respiratory failure 5 (24%) Most common IARs -subcutaneous skin disorders 13/21 (62%) -vascular disorders 10/21 (48%) -blood pressure increases 7/21 (33%) Heart/respiratory rate increases 7/21 (33%) Death 6/21 (29%)		**Risk of Bias (low/high/unclear)**: Selection Bias: (High) Non-randomized; broader study population than inclusion criteria stated (older, younger) Performance Bias: (High) Open label study design with no blinding of most study personnel Detection Bias: (Unclear) LVH assessment was confirmed by a central, blinded cardiologist but no details; interim analysis performed at 26 weeks Attrition Bias: (Low) No withdrawals reported Reporting Bias: (Unclear) KM analysis may have overestimated benefit; no rationale for censored patients described; actual values for some secondary outcomes not reported Other Bias: (High) Funded by manufacturer. Primary authors received editorial assistance from Genzyme. **Applicability**: Patient: Patients with IOPD Intervention: alglucosidase alfa 20 mg/kg IV up to 40 mg/kg IV Comparator: None (historical) Limits conclusions regarding efficacy of treatment or long-term safety. Functional outcomes also compared to historical control. No patient to patient matching occurred for historical control and important markers of disease progression were not reported including pulmonary function details and non-pharmacological therapy (e.g., assistive devices, ventilator support, etc). Outcomes: Survival Setting: Multinational (US, France, Israel, UK)

Abbreviations: AIMS = Alberta Infant Motor Scale; AE = adverse events; ARR = absolute risk reduction; CI = confidence interval; DB = double blinded; Dx = diagnosis; ERT = enzyme replacement therapy; FVC = forced vital capacity; GAA = enzyme alpha glucosidase; IARs = Infusion Associated Reactions; IOPD = infantile onset Pompe disease; ITT = intention to treat; IV = intravenous; IVRS = interactive voice response system KM = Kaplan-Meier; L = liters; LOCF = last observation carried forward; LOPD = Late onset; PC = placebo controlled; Pompe disease; LVH = left ventricular hypertrophy; LVMI = left ventricular mass index; MC = multicenter; mITT = modified intention to treat; M = meter; Mo = months; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OL = open label; PDMS-2 = Peabody Developmental Motor Scale; PP = per protocol; QMT = quantitative muscle testing; SAEs = serious adverse events; TEAEs = treatment emergent adverse events; UK = United Kingdom; US = United States; 6MWT= six minute walk test

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

LUMIZYME® (alglucosidase alfa), for injection, for intravenous use

Initial U.S. Approval: 2010

WARNING: RISK OF ANAPHYLAXIS, HYPERSENSITIVITY AND IMMUNE-MEDIATED REACTIONS, AND RISK OF CARDIORESPIRATORY FAILURE

See full prescribing information for complete boxed warning.

- **Life-threatening anaphylactic reactions and severe hypersensitivity reactions have occurred in some patients during and after alglucosidase alfa infusions. Immune-mediated reactions presenting as proteinuria, nephrotic syndrome, and necrotizing skin lesions have occurred in some patients following alglucosidase alfa treatment. Closely observe patients during and after alglucosidase alfa administration and be prepared to manage anaphylaxis and hypersensitivity reactions. Inform patients of the signs and symptoms of anaphylaxis, hypersensitivity reactions, and immune-mediated reactions and have them seek immediate medical care should signs and symptoms occur. (5.1, 5.2)**
- **Infantile-onset Pompe disease patients with compromised cardiac or respiratory function may be at risk of serious acute exacerbation of their cardiac or respiratory compromise due to fluid overload, and require additional monitoring. (5.3)**

----------RECENT MAJOR CHANGES----------

Warnings and Precautions (5.2, 5.5, 5.6) 02/2020

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

LUMIZYME® (alglucosidase alfa) is a hydrolytic lysosomal glycogen-specific enzyme indicated for patients with Pompe disease (GAA deficiency). (1)

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

- 20 mg per kg body weight administered every 2 weeks as an intravenous infusion. (2)

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

- For injection: 50 mg of alglucosidase alfa as lyophilized powder in a single-use vial for reconstitution. (3)

----------CONTRAINDICATIONS----------

None. (4)

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

- Anaphylaxis and Hypersensitivity Reactions: Life-threatening anaphylaxis and hypersensitivity reactions have been observed in some patients during and after treatment with alglucosidase alfa. Ensure that appropriate medical support measures, including cardiopulmonary resuscitation equipment, are readily available. If anaphylaxis or severe hypersensitivity reactions occur, immediately discontinue infusion and initiate appropriate medical treatment. (5.1)
- Immune-Mediated Reactions: Monitor patients for the development of systemic immune-mediated reactions involving skin and other organs. (5.2)
- Risk of Acute Cardiorespiratory Failure: Patients with compromised cardiac or respiratory function may be at risk of acute cardiorespiratory failure. Caution should be exercised when administering alglucosidase alfa to patients susceptible to fluid volume overload. Appropriate medical support and monitoring measures should be available during infusion. (5.3)
- Risk of Cardiac Arrhythmia and Sudden Cardiac Death during General Anesthesia for Central Venous Catheter Placement: Caution should be used when administering general anesthesia for the placement of a central venous catheter intended for alglucosidase alfa infusion. (5.4)
- Risk of Antibody Development: Patients with infantile-onset Pompe disease should have a cross-reactive immunologic material (CRIM) assessment early in their disease course and be managed by a clinical specialist knowledgeable in immune tolerance induction in Pompe disease to optimize treatment. (5.5)

----------ADVERSE REACTIONS----------

The most frequently reported adverse reactions (≥5%) in clinical trials were hypersensitivity reactions and included: anaphylaxis, rash, pyrexia, flushing/feeling hot, urticaria, headache, hyperhidrosis, nausea, cough, decreased oxygen saturation, tachycardia, tachypnea, chest discomfort, dizziness, muscle twitching, agitation, cyanosis, erythema, hypertension/increased blood pressure, pallor, rigors, tremor, vomiting, fatigue, and myalgia (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: 02/2020

Alglucosidase alfa

Goal(s):

- Ensure medically appropriate use of alglucosidase alfa for the treatment of Pompe disease

Length of Authorization:

Up to 12 months

Requires PA:

- Alglucosidase 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

Indication	Dosing Regimen
Pompe Disease	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.
3. Is the request for continuation of therapy previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. 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 #5	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Is this request from a metabolic specialist, biochemical geneticist, or has provider documented experience in the treatment of Pompe disease?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the agent dosed appropriately based on documentation of patient weight taken within the past month? (**see Table 1**)	**Yes:** Document patient weight and go to #7. Weight: _____	**No:** Pass to RPh. Deny; medical appropriateness.
7. Is the request for treatment of infantile-onset Pompe disease (IOPD)?	**Yes:** Go to #8	**No:** Go to #11
8. Has the provider documented a baseline value for ALL the following assessments? • Muscle weakness/Motor function? (e.g. AIMS, PDMS-2, Pompe PEDI, etc) • Respiratory status? • Cardiac imaging (e.g. chest x-ray, echocardiography)? • CRIM status?	**Yes:** Document baseline results and go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Is the patient CRIM-negative?	**Yes:** Go to #10	**No:** Approve for 3 months If approved, a referral will be made to case management by the Oregon Health Authority.
10. 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
11. Is the patient at least 5 years of age or older?	**Yes:** Go to #12	**No:** Go to #13

Approval Criteria		
12. Is there a baseline documentation for both of the following? • Pulmonary function test (PFT) with spirometry including baseline percent predicted forced vital capacity (FVC) value 30 to 79% of predicted value while in the sitting position • Demonstration of completed 6-minute walk test (6MWT) of at least 40 meters with or without an assistive device -OR- Muscle weakness in the lower extremities?	**Yes:** Approve for 6 months Document baseline results. If approved, a referral will be made to case management by the Oregon Health Authority.	**No:** Pass to RPh. Deny; medical appropriateness
13. Has the provider documented a baseline value for both the following assessments: • Muscle weakness/Motor function? (e.g. AIMS, PDMS-2, Pompe PEDI, etc) • Respiratory status?	**Yes:** Approve for 3 months Document baseline results. If approved, a referral will be made to case management by the Oregon Health Authority.	**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 the first renewal of alglucosidase alfa therapy?	**Yes:** Go to #3	**No:** Go to #4

Renewal Criteria		
3. Is there documentation that the patient has recently been tested* for IgG antibody formation? * = *Patients should be monitored for IgG antibody formation every 3 months for 2 years and then annually thereafter per manufacturer labeling.*	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Compared to baseline measurements, is there documented evidence of improvement or stabilization in muscle, motor, and/or respiratory function?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the agent dosed appropriately based on documentation of patient weight taken within the past month? (**see Table 1**)	**Yes:** Document patient weight and go to #6 Weight: _____	**No:** Pass to RPh. Deny; medical appropriateness
6. Is patient under 5 years old?	**Yes:** Approve for 3 months	**No:** Go to #7
7. Has the patient received alglucosidase alfa for at least 6 months?	**Yes:** Approve for 12 months	**No:** Approve for 3 months