Subject: Lumizyme, Myozyme (Alglucosidase alfa)	**Original Effective Date:** 1/2016
Policy Number: MCP-267	**Revision Date(s):**
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MCPC Approval Date: 7/10/2018	

DISCLAIMER

This Medical Policy is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina Clinical Policy (MCP) document and provide the directive for all Medicare members.

SUMMARY

This policy addresses the coverage of **Alglucosidase alfa (Lumizyme, Myozyme)** treatment of patients with Pompe disease when appropriate criteria are met.

- Pompe disease is a rare progressively debilitating and often fatal inherited disorder of glycogen metabolism caused by the absence or marked deficiency of the lysosomal enzyme GAA. [a,4,5,6] In the infantile-onset form, Pompe disease results in intralysosomal accumulation of glycogen in various tissues, particularly cardiac and skeletal muscle and the liver, resulting in the development of cardiomyopathy, progressive muscle weakness, hepatomegaly, and impaired respiratory function; death secondary to cardiorespiratory failure usually occurs in the first year of life. [a,4,5,6]

- Lumizyme and Myozyme are proprietary names for alglucosidase alfa, a recombinant form of the enzyme acid alpha-glucosidase, which is required for glycogen cleavage. These enzyme preparations are indicated for use in patients with Pompe disease. As per action by the FDA, the use of Lumizyme has been expanded to permit use in all Pompe patients. There is no limitation as to age and phenotype as per previous prescribing restrictions. In addition, the Risk Mitigation Evaluation Strategy (REMS) program has been removed. Lumizyme still has a boxed warning regarding serious adverse reactions.

- Based on newly available biochemical and clinical data, the FDA has concluded that Lumizyme and Myozyme are chemically and biochemically comparable. Consequently, the safety and effectiveness of Lumizyme and Myozyme are expected to be comparable.[i]

- Alglucosidase alfa improves ventilator-free survival in patients with infantile-onset Pompe disease as compared with an untreated historical control group.[a,4]
  - Safety and efficacy in patients with forms of Pompe disease other than infantile-onset *not* established.[a]
  - It is noted that alglucosidase alfa Appears to have strongest and most consistent therapeutic effect on the cardiorespiratory manifestations of Pompe disease;[5,6] effects on motor function appear highly dependent on patient's condition at start of treatment.[5,6]
  - Effect of treatment on motor function over time unknown.[a]

- A guideline based on the available evidence and consensus recommendations of specialists experienced in the treatment of late-onset Pompe disease recommend initiating treatment with ERT at the onset of symptoms and to re-evaluate annually to reassess whether treatment should continue.[B]

- **Hayes** At the time of this writing, a Hayes assessment addressing Pompe disease [acid alpha-glucosidase (GAA) deficiency] or corresponding indications was not located or unavailable.

CLASSIFICATION: Metabolic Agents; Endocrine and Metabolic Agents; human enzyme (glycoprotein)

FDA INDICATIONS

- **Pompe disease:** For use in patients with Pompe disease (acid alpha-glucosidase deficiency)[a,b]

FDA expands approval of Pompe disease drug [August 2014]
The FDA approved the lysosomal glycogen-specific enzyme alglucosidase alfa (*Lumizyme*) for the treatment of infantile-onset Pompe disease, including in patients younger than age 8. This approval eliminates previous restrictions on the drug's use to late (non-infantile) onset Pompe disease in patients 8 years of age and older.[i]

Approval was based on new data demonstrating similarities between *Lumizyme* and *Myozyme*, which is already approved for use in younger patients, and on a study of 18 patients with infantile-onset Pompe disease that showed similar improvements in ventilator-free survival as patients treated with *Myozyme*. The new agent will carry a boxed warning on the risk for anaphylaxis, severe allergic reactions, immune-mediated reactions, and cardiorespiratory failure.[i]

The FDA reviewed newly available information and determined that Lumizyme and Myozyme are chemically and biochemically comparable.[i] Consequently, the safety and effectiveness of Lumizyme and Myozyme are expected to be comparable. In addition, a single-center clinical study of 18 infantile-onset Pompe disease patients, aged 0.2 to 5.8 months at the time of first infusion, provides further support that infantile-onset patients treated with Lumizyme will have a similar improvement in ventilator-free survival as those treated with Myozyme.

Limitations of use:

Myozyme: Improves ventilator-free survival in patients with **infantile-onset** Pompe disease compared with an untreated historical control, whereas use of **Myozyme** in patients with other forms of Pompe disease has not been adequately studied to ensure safety and efficacy.[a]

Available as: Single use vial: 50 mg lyophilized powder (cake) for injection that requires reconstitution prior to infusion.

**Both Myozyme and Lumizyme are manufactured by Genzyme Corporation, but at different manufacturing sites and under separate biologic license applications (BLA). Based on newly available biochemical and clinical data, the FDA has concluded that Lumizyme and Myozyme are chemically and biochemically comparable. Consequently, the safety and effectiveness of Lumizyme and Myozyme are expected to be comparable.*

FDA Approval Date

- Myozyme (for infantile-onset Pompe disease): On April 28, 2006, the FDA approved alglucosidase alfa, rhGAA (Myozyme), the first treatment for IPD. Alglucosidase alfa had been granted FDA orphan drug status and was approved under a priority review.
- Lumizyme (for patients 8 years and older): Under a priority review, the FDA approved alglucosidase alfa (Lumizyme®) as an orphan drug on May 10, 2010.
- Lumizyme (for all patients with Pompe disease; for use in all patients with infantile-onset Pompe disease): August 2014

Boxed Warning

- Boxed warning (Myozyme and Lumizyme): Life-threatening anaphylactic reactions, severe allergic reactions and immune mediated reactions have been observed in some patients during Myozyme and Lumizyme infusions.
- Boxed warning (Myozyme and Lumizyme): Patients with compromised cardiac or respiratory function may be at risk of serious acute exacerbation of their cardiac or respiratory compromise due to infusion reactions, and require additional monitoring.

Risk Evaluation and Mitigation Strategy (REMS)

Because data were submitted supporting approval of Lumizyme for all Pompe patients, a REMS restricting its use to a specific age group is no longer necessary. While the risk of anaphylaxis, severe allergic reactions, and severe cutaneous and immune mediated reactions for Lumizyme still exist, these risks are comparable to Myozyme and are communicated in labeling through the Warnings and Precautions, and a Boxed Warning.

As of August 1, 2014, the FDA no longer requires a REMS program for this product. REMS known as Lumizyme ACE (Alglucosidase Alfa Control and Education) Program eliminated due to expanded approval [FDA Press Release 2014 Aug 1: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm407563.htm] Health care professionals, healthcare facilities, and patients will no longer be required to enroll in the Lumizyme REMS program to be able to prescribe, dispense, or receive Lumizyme.

Full details of the alglucosidase alfa (Lumizyme) REMS program can be reviewed by visiting the Lumizyme Alglucosidase Control and Education (ACE) Program Web site http://www.lumizyme.com/ACE/ or contacting Genzyme

RECOMMENDATIONS/COVERAGE CRITERIA

Alglucosidase alfa (Lumizyme, Myozyme) may be authorized for members who meet **ALL** of the following criteria

1. Prescriber specialty [ONE]

- ❒ Prescribed by, or in consultation with, a metabolic specialist, endocrinologist, biochemical geneticist, or physician experienced in the management of physician who specializes in Pompe disease. Submit consultation notes if applicable.
  NOTE: Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

2. Diagnosis/Indication [ALL]

The indicated diagnosis (including any applicable labs and /or tests) should be supported by documentation from the member's medical records.

NOTE: Pompe disease is confirmed via genetic sequencing through biochemical and genetic testing confirming the diagnosis requires demonstration of absent or reduced acid alpha-glucosidase (GAA) enzyme activity.[3]

- ❒ Prescribed in accordance to label indication: [ONE]
  - ❍ Myozyme: For diagnosis of Infantile-onset Pompe disease (Acid alpha-glucosidase (GAA) deficiency)
  - ❍ Lumizyme: For diagnosis of Pompe disease (GAA deficiency)

- ❒ Diagnosis of Pompe disease supported by identification of acid alpha-glucosidase activity deficiency in cultured skin fibroblasts or peripheral blood lymphocytes or skin biopsy, or muscle. Documentation required.

- *Pompe disease is confirmed via genetic sequencing through biochemical and genetic testing confirming the diagnosis requires demonstration of absent or reduced acid alpha-glucosidase (GAA) enzyme activity.*[3]

❒ One or more clinical signs or **symptoms** of Pompe disease, including but not limited to: [AT LEAST ONE]
- ❍ Readily observed evidence of glycogen storage (macroglossia, hepatomegaly, normal or increased muscle bulk)
- ❍ Involvement of respiratory muscles manifesting as respiratory distress (e.g., tachypnea)
- ❍ Profound diffuse hypotonia
- ❍ Proximal muscle weakness
- ❍ Reduced forced vital capacity (FVC) in upright or supine position

- *The population for which the approval of alglucosidase alfa was approved on had clinical manifestations of Pompe disease [e.g. hypotonia, cardiac hypertrophy, muscle weakness of lower extremities, or low predicted force vital capacity (FVC)]. There is currently no high quality evidence indicating that treating asymptomatic patients with Pompe disease leads to a reduced risk of long term clinical outcomes such as mortality.*
- *In a consensus statement for individuals with late-onset Pompe disease, enzyme replacement therapy (ERT) was not recommended for individuals who had no symptoms or objective signs (proximal muscle weakness or reduced FVC in either upright or supine position) of Pompe disease.*[B] *ERT was recommended for individuals with confirmed Pompe disease and demonstrable muscle weakness or reduction in pulmonary function. The decision to continue ERT is complex and is individualized during routine neuromuscular clinic visits with the treating physician (Cupler, 2012).*

3. Age/Gender/Other restrictions [ALL]

❒ No evidence of cardiac hypertrophy[a,b]
- *Cardiorespiratory failure has been observed in patients with cardiac hypertrophy up to 72 hours after infusion; arrhythmias have also been observed in patients with cardiac hypertrophy.*[a,b]

❒ For Myozyme only: Infantile onset Pompe disease; children 1 month to 3.5 years of age [AS APPLICABLE]
- *Pediatric patients aged 1 month to 3.5 years at time of first infusion have been treated with Myozyme in clinical trials. Other open-label clinical trials of Myozyme have been performed in older pediatric patients ranging from 2 to 16 years at the initiation of treatment (juvenile-onset Pompe disease); however, the risks and benefits of Myozyme treatment have not been established in the juvenile-onset Pompe disease population.*[a]

4. Step/Conservative Therapy/Other condition Requirements [ALL]

❒ Baseline pulmonary function testing (PFT) and muscle strength evaluation. ***Required for continuation of treatment requests as clinical documentation of stabilization, lack of disease progression or continued improvement***
EXCEPTION: Prescriber submit documentation for children 6 years or older who are not able to voluntarily perform the physiological maneuvers required for the pulmonary function tests (PFTs) for Medical/Pharmacy Director review. **[MEDICAL/PHARMACY DIRECTOR REVIEW REQUIRED]**

❒ Member's cardiac and respiratory function (e.g., cardiac disease, heart failure, respiratory insufficiency, respiratory illness, sepsis) has been considered for members with compromised cardiac and/or respiratory function. Documentation required. [AS APPLICABLE]
- *Alglucosidase alfa (Lumizyme, Myozyme) carries a boxed warning regarding the risk of cardiorespiratory failure. Patients with compromised cardiac and/or respiratory function (e.g.,*

cardiac disease, heart failure, respiratory insufficiency, respiratory illness, sepsis) may be at risk for serious acute exacerbation of their cardiac or respiratory status due to fluid overload. These patients require additional monitoring. Patients with advanced Pompe disease often have underlying compromised cardiac and respiratory function and should be monitored more closely.

- ❒ **For late-onset Pompe disease:** Prescriber has considered and prescribed other treatment options *for late-onset Pompe disease* including diet modification (high protein, low carbohydrate), exercise, and supportive care (e.g. mechanical ventilation for respiratory failure).[E] Documentation required.

- ❒ Member will be monitored for IgG antibody formation every 3 months for 2 years and then annually thereafter
  - ➢ *The manufacturer recommends monitoring for IgG antibody formation every 3 months for 2 years, then annually. Consider testing if patient develops allergic or other suspected immune-mediated reaction or experiences loss of clinical response.*
  - ➢ *No commercial tests are available; however, sampling kits can be obtained by contacting Genzyme Corporation at 1-800-745-4447. Patients who experience anaphylactic or allergic reactions may also be tested for IgE antibodies to alglucosidase alfa and other mediators of anaphylaxis.*[a,b]

5. Contraindications*/Exclusions/Discontinuations

**FDA–approved labeling lists no contraindications to therapy with alglucosidase alfa.*[a]

Authorization will <u>not</u> be granted if ANY of the following conditions apply [ANY]

- ❒ Non-FDA approved indications
- ❒ Hypersensitivity to alglucosidase alfa

<u>Exclusions</u> [ANY]

- ❒ Member does not meet or Prescriber has not submitted ALL documentation required

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit medical records and specific labs, chart notes, and documentation as indicated in the criteria above. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

- ❒ Prescribers are required to indicate the following on PA amendment requests for Lumizyme or Myozyme:
  - ❍ Member's current weight
  - ❍ Lumizyme or Myozyme dose requested

CONTINUATION OF THERAPY

Alglucosidase alfa (Lumizyme, Myozyme) may be authorized for continuation of therapy if meet **ALL** of the following criteria are met: **[ALL]**

1. Initial Coverage Criteria

- ❑ Member currently meets ALL initial coverage criteria
- ❑ Consultation notes submitted for initial and continuation of treatment requests at least ONCE annually
  - ➢ *American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) recommendations based on the available evidence and consensus recommendations of specialists experienced in the treatment of late-onset Pompe disease recommend initiating treatment with ERT at the onset of symptoms and to re-evaluate annually to reassess whether treatment should continue.*[B]

2. Compliance

- ❑ Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history (review Rx history for compliance), including:
  - ❍ Adherent to the prescribed medication regimen
  - ❍ Tolerance to therapy
  - ❍ No severe adverse reactions or drug toxicity

NOTE: Therapy may be discontinued due to poor adherence upon recommendation of the Molina Medical Director when adherence < 85% has been demonstrated in at least two months during the course of therapy

NOTE: History of non-compliance or non-adherence as verified by member's medication fill history or prescription drug profile may result in continuation of therapy request not being authorized. [MOLINA MEDICAL/PHARMACY REVIEWER TO VERIFY

- ❒ Monitoring for IgG antibody formation as recommended (every 3 months for 2 years, then annually)
  - ➢ *The manufacturer recommends monitoring for IgG antibody formation every 3 months for 2 years, then annually. Consider testing if patient develops allergic or other suspected immune-mediated reaction or experiences loss of clinical response. No commercial tests are available; however, sampling kits can be obtained by contacting Genzyme Corporation at 1-800-745-4447. Patients who experience anaphylactic or allergic reactions may also be tested for IgE antibodies to alglucosidase alfa and other mediators of anaphylaxis.*[a-e]
  - ➢ *The presence of IgG antibodies has been observed within 3 months from the onset of therapy in the majority of patients. High and sustained IgG antibody titers may result in reduced efficacy of alglucosidase alfa (eg, loss of motor function, ventilator dependence, death). Regularly monitor all patients for development of IgG antibodies; consider testing for IgG titers in patients who develop hypersensitivity reactions, other immune-mediated reactions, or loss of clinical response. Patients with reduced clinical response may also be tested for inhibitory antibody activity.*

3. Labs/Reports/Documentation required [ALL APPLICABLE]

- ❒ Clinical documentation of **stabilization, lack of disease progression or continued improvement** as evidenced by results of appropriate monitoring studies [compared to baseline measurements], including but not limited to: [ALL APPLICABLE]
  - ❍ Upright and supine PFT's
  - ❍ Muscle strength evaluations [i.e. does not exhibit signs of decreasing motor activity (e.g. muscle strength evaluations]
  - ❍ Echocardiograms

4. Discontinuation of Treatment [ANY]

Discontinue treatment if ANY of the following conditions applies: [ANY]

- ❑ Intolerable adverse effects or drug toxicity
- ❑ Persistent and uncorrectable problems with adherence to treatment
- ❑ Poor response to treatment as evidenced by physical findings and/or clinical symptoms
- ❑ Contraindications/Exclusions to therapy
  - ❍ Non-FDA approved indications
  - ❍ Hypersensitivity to alglucosidase alfa

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

1. Recommended Dosage [ALL]

The recommended dose of Alglucosidase alfa (Lumizyme, Myozyme) is 20 mg/kg of body weight administered every 2 weeks as an intravenous infusion.[a-e] The total volume of infusion is determined by the patient's body weight and should be administered over approximately 4 hours.

- ❒ **Adult:** Pompe disease (Lumizyme): The recommended dosage of Lumizyme is **20 mg/kg body weight administered every two weeks** as an intravenous infusion.
  - ➢ *Studies have not demonstrated superior clinical benefit in patients receiving of 40 mg/kg every 2 weeks dosing versus those who received 20mg/kg every 2 weeks.*[b]
  - ➢ *Lumizyme is intended for intravenous infusion. It is supplied in 50mg vials as a lyophilized powder for reconstitution. When reconstituted as directed, the reconstituted solution contains a total extractable volume of 10 ml at 5 mg/ml alglucosidase.*

- ❒ **Pediatric:** Pompe disease (Lumizyme, Myozyme): 20 mg/kg IV every 2 weeks[a,b]

2. Authorization Limit [ALL]

- ❒ Quantity limit: [ALL]
  - ❍ Max dose not exceeding 20mg/kg every 2 weeks
  - ❍ 26 infusions per year based on a total dose of less than or equivalent to 20mg/kg every 2 weeks
- ❒ If a member's weight changes, resulting in a change in dose for Lumizyme or Myozyme, a prior authorization request must be submitted to increase dosage and the following information must be submitted for Lumizyme or Myozyme:
  - ❍ Member's most recent weight and the date this weight was measured
  - ❍ Lumizyme or Myozyme dose calculation
- ❒ Dispensing limit: ONE (1) dose at a time
- ❒ Duration of initial authorization: May be authorized up to **6 months**
- ❒ Continuation of treatment: Re-authorization for continuation of treatment is required every six (6) months to determine continued need based on documented positive clinical response. Documentation by chart notes of disease stability or improvement in symptoms must be provided.
  - ➢ A guideline based on the available evidence and consensus recommendations of specialists experienced in the treatment of late-onset Pompe disease recommend initiating treatment with ERT at the onset of symptoms and to re-evaluate annually to reassess whether treatment should continue.[B]
- ❒ Duration of continuation of treatment: May be authorized up to **12 months**

3. Route of Administration [ALL]

- ❒ Alglucosidase alfa is considered **provider-administered** with appropriate medical support is readily available in the event of anaphylaxis, severe allergic reaction, or acute cardiorespiratory failure. Molina Healthcare recommends alternative sites of care (such as physician's offices, infusion centers, and home infusion) which are well-established in the administration of these agents.

- ❒ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare. Self-administered medications may not be dispensed for self-administration and billed through the medical benefit by a provider; they must be dispensed through a participating pharmacy.

COVERAGE EXCLUSIONS

This policy only addresses the indication of Alglucosidase alfa (Lumizyme, Myozyme) for the treatment of Pompe disease [acid alpha-glucosidase (GAA) deficiency] when appropriate criteria are met.

All other uses of Alglucosidase alfa (Lumizyme, Myozyme) that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

SUMMARY

Pompe disease is a rare autosomal recessive disorder caused by a deficiency of the lysosomal enzyme alpha-glucosidase responsible for degrading glycogen causing glycogen to accumulate in muscle and other tissues.[A-D] The result is intralysosomal accumulation of glycogen, primary in muscle cells, that leads to a progressive loss of muscle function. Accumulation of glycogen in muscle cells can lead to movement and breathing difficulties.

Pompe disease occurs in an estimated 1 in every 40,000 to 300,000 births.i Its primary symptom is heart and skeletal muscle weakness, progressing to respiratory weakness and death from respiratory failure.

Pompe disease is a progressive, multisystemic, debilitating, and often fatal neuromuscular disorder. It was first defined in 1932 by Dutch pathologist Joannes C. Pompe in a seven-month-old infant who died of idiopathic cardiac hypertrophy and was found to have massive glycogen* accumulation in many tissues, but predominantly skeletal and cardiac muscles.[7]
**Glycogen: Large branched polysaccharide consisting of glucose residues. The major carbohydrate reserve of animals, stored primarily in liver and muscle, synthesized and degraded for energy as demanded.*

Pompe disease is also referred to as:[7]

- Acid maltase deficiency (AMD)
- Glycogen storage disease (GSD) type II
- Glycogenosis type II
- Acid alpha-glucosidase (GAA) deficiency
- Lysosomal alpha-glucosidase deficiency

Pompe disease is generally considered in two forms and can present as infantile or late-onset form:

1. Infantile-onset
    - A progressive, multisystem disorder that causes hypotonia and feeding difficulties in the first year of life. The disease affects cardiac, skeletal and smooth muscles, the pulmonary and gastrointestinal systems, and anterior horn cells. Death due to cardiorespiratory failure typically occurs in the first year of life.[3]
    - Pompe disease results in intralysosomal accumulation of glycogen in various tissues, particularly cardiac and skeletal muscles and hepatic tissues, leading to the development of cardiomyopathy, progressive muscle weakness and impairment of respiratory function.
    - Symptoms of cardiomyopathy and a generalized lack of muscle tone generally appear during the first few months of life. Without treatment, most patients with classic infantile form deteriorate with death during the first one to two years of life from cardiac insufficiency due to cardiac muscle dysfunction.

2. Late onset (juvenile- and adult-onset) forms:
    - Intralysosomal accumulation of glycogen is limited primarily to skeletal muscle, resulting in progressive muscle weakness. Death in all forms is usually related to respiratory failure.

- May be present at any age. The primary symptom is skeletal muscle myopathy. Over time this results in progressive muscle weakness and death usually related to respiratory failure.

There are no cures at this time. Diet therapy and enzyme replacement therapy may be highly effective at reducing clinical manifestations. In some patients, liver transplantation may abolish biochemical abnormalities.

The goals of pharmacotherapy are to reduce morbidity and prevent complications.

PHARMACOLOGIC AGENTS/CONVENTIONAL THERAPY

Alglucosidase alfa (**Lumizyme**, **Myozyme**) is an enzyme replacement therapy (ERT) orphan drug for treatment of Pompe disease (Glycogen storage disease type II), a rare lysosomal storage disorder (LSD).[4]

Alglucosidase alfa is a recombinant form of the enzyme [acid alpha glucosidase (GAA)], which is required for glycogen cleavage. Lumizyme is produced by recombinant DNA technology in a Chinese hamster ovary cell line. The Lumizyme manufacturing process differs from that for Myozyme, resulting in differences in some product attributes. Alglucosidase alfa degrades glycogen by catalyzing the hydrolysis of α-1,4- and α-1,6 glycosidic linkages of lysosomal glycogen. Due to an inherited acid alpha-glucosidase deficiency or absence, glycogen accumulates in the tissues of patients with Pompe disease, leading to progressive muscle weakness. In infantile-onset Pompe disease, glycogen accumulates in cardiac and skeletal muscles and hepatic tissue, leading to cardiomyopathy and respiratory failure. Juvenile- and adult-onset Pompe disease are limited to glycogen accumulation in skeletal muscle, leading to respiratory failure. Alglucosidase alfa binds to mannose-6-phosphate receptors on the cell surface, is internalized, and transported to lysosomes where it is activated for increased enzymatic glycogen cleavage.[a-e]

Currently, Lumizyme and Myozyme are two marketed preparations of alglucosidase alfa ERTs for Pompe disease in the United States. Alglucosidase alfa was designated as an orphan drug for the treatment of Pompe disease in 1997; alglucosidase alfa (Myozyme) was approved by the FDA for the treatment of infantile-onset Pompe disease in April 2006. Lumizyme was approved by the FDA for patients 8 years and older with late (non-infantile) onset Pompe disease who do not have evidence of cardiac hypertrophy in May 2010; in August 2014, FDA approval was expanded to include all patients with Pompe disease.

PIVOTAL TRIALS

Lumizyme (alglucosidase alfa)

Lysosomal alpha-1,4-glucosidase deficiency: Infantile onset

Alglucosidase alfa was not superior in terms of survival when compared with untreated historical controls in a 52-week interim analysis of a clinical trial. In another study, 16 of 21 patients with infantile-onset Pompe disease (3 months to 3.5 years at first infusion) remained alive and 10 were free of invasive ventilatory support after 52 weeks of alglucosidase alfa therapy. In a second study, 16 of 18 patients (0.2 to 5.8 months at first infusion) were alive at 18 months of age without invasive ventilator support.
In small open-label studies, recombinant human acid alpha-glucosidase (rhGAA) therapy has been correlated with improved cardiac and skeletal muscle function in infants with glycogen storage disease type II (Pompe disease).

Lysosomal alpha-1,4-glucosidase deficiency: Juvenile onset

In a randomized trial (N=90) of treatment-naive patients with late-onset Pompe disease, alglucosidase alpha therapy significantly increased the distance walked on a 6-minute test and improved the forced vital capacity by 3.4% compared with placebo

Alglucosidase alfa (Lumizyme®) is FDA-approved for individuals with Pompe disease (GAA deficiency). The safety and efficacy was assessed in 57 treatment-naïve individuals with infantile-onset Pompe disease, aged 0.2 months to 3.5 years at first infusion, in three separate clinical trials. In all three trials ventilator-free survival improved significantly compared

with an untreated historical control. The safety and efficacy of alglucosidase alfa (Lumizyme®) was also assessed in 90 individuals with juvenile/adult-onset Pompe disease in a randomized, double-blinded, placebo-controlled trial. Alglucosidase alfa (Lumizyme®) was shown to have a significant increase in forced vital capacity (FVC) and the distance an individual with juvenile/adult-onset Pompe disease can walk within 6 minutes (6 minute walk test).

Three open-label controlled studies evaluated alglucosidase alfa in 57 treatment naïve patients aged 0.2 months to 3.5 years with infantile-onset Pompe disease treated for 52 to 104 weeks.[b]

- Primary outcomes assessed were death and the need for invasive ventilator support.
- All studies demonstrated a significant survival benefit, with 76% to 88% of subjects alive at the time of the primary efficacy analysis. Historical controls were used to compare relative efficacy of alglucosidase alfa to no treatment in one study. Two percent of historical controls were alive at the same point in time as the primary efficacy endpoint (18 months). In all the trials, a minority of patients required invasive ventilator support, which ranged from 0% to 17% of subjects treated with alglucosidase alfa.
- One of the pivotal trials evaluated 20mg/kg and 40mg/kg dosing of alglucosidase alfa in patients with infantile-onset Pompe disease. No difference in efficacy (i.e. survival) was noted for either dose.
- The precision of the study results is uncertain due to the absence of a control group in two of the studies, and the use of a historical control group in one of the studies.

One high quality systematic review of 21 studies evaluated the use of alglucosidase alfa in a total of 368 patients with late-onset Pompe disease.[2]

- The top four outcomes with the most data included reduction in creatinine kinase levels (n=138), increased motor performance as measured by the six minute walk test (n=122), improved respiratory status as measured by forced vital capacity (n=124), and the reduction in need for ventilator support (n=66).
- Although quality of life was assessed in some trials, no assessment tools have been designed to specifically measure the impact of clinical improvements on quality of life in patients with late-onset Pompe disease.
- Results for all four endpoints demonstrated improvement or stability in a majority of patients receiving alglucosidase alfa. The percent of subjects showing improvement or stability in creatinine kinase, motor performance, respiratory status and duration of ventilator support were 81%, 86%, 65.3%, and 95.5% respectively.
- The studies included in the systematic review were of low quality as study populations were small (n<90), most studies evaluated surrogate endpoints, and retrospective studies were included in the systematic review (case reports, observational studies, and statistical analyses) undermining the certainty in the evidence of clinical benefit.

American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) recommendations for ERT in patients with for late-onset Pompe disease[B]

- ERT not recommended for patients with confirmed disease on screening but without disease symptoms or objective signs, but monitor every 6 months and start ERT at onset of any symptoms or objective signs
- ERT recommended for
  - presymptomatic patients (confirmed disease on screening) without objective signs but who have any of
    - onset of disease symptoms
    - onset of detectable proximal muscle weakness
    - onset of reduced forced vital capacity when upright or supine
  - presymptomatic patients (confirmed disease on screening) with objective signs
    - proximal muscle weakness detectable on Medical Research Council scale
    - reduced forced vital capacity when upright or supine
  - symptomatic patients, regardless of use of noninvasive ventilation, with any of
    - increased limb weakness
    - reduction in forced vital capacity when upright or supine
    - weakness leading to difficulty completing activities of daily living
  - patients with severe symptoms (confined to wheelchair and using invasive ventilation during day and at night)

- ERT duration 1 year is reasonable, followed by evaluation of treatment efficacy to determine continuation of presumed long-term or life-long treatment
- monitor all patients for IgG antibodies every 3 months for 2 years, then annually

MYOZYME

In 2006, the FDA approved the biologics license application for alglucosidase alfa (Myozyme) to treat individuals with Pompe disease (GAA deficiency). The 2014 FDA Product Information Label states:

> Myozyme has been shown to improve ventilator-free survival in patients with infantile-onset Pompe disease as compared to an untreated historical control, whereas use of Myozyme in patients with other forms of Pompe disease has not been adequately studied to assure safety and efficacy.

An international, multicenter, open-label clinical trial of eligible children with infantile-onset Pompe disease treated with Myozyme compared clinical outcomes to 61 historical controls. Eighteen enrolled children were randomized to either 20 mg/kg or 40 mg/kg of Myozyme every 2 weeks, with length of treatment ranging from 52 – 106 weeks. Enrollment criteria included individuals with documented infantile-onset Pompe disease, including skin fibroblast GAA activity <1% of the normal mean and hypertrophic cardiomyopathy (left ventricular mass index greater than or equal to 65g/m^2 by echocardiogram); and individuals were no older than 26 weeks at enrollment. Exclusion criteria included respiratory insufficiency (oxygen saturation <90% or CO_2 partial pressure >55 mmHg [venous] or >40mm Hg [arterial] on room air, any ventilator use), or any prior GAA treatment (Kishnani, 2007).[4]

Efficacy was measured by comparing the number of Myozyme-treated individuals who died or needed invasive ventilator support with the mortality experienced by a historical cohort of individuals with untreated infantile-onset Pompe disease with similar age and disease severity. By the age of 18 months, only 1 of the 61 historical controls was alive (98% mortality), indicating the poor outcome of individuals who are left untreated. Within the first 12 months of treatment, 3 of 18 individuals treated with Myozyme required invasive ventilatory support (17%, with 95% confidence interval [CI] 4% to 41%); there were no deaths. With continued treatment beyond 12 months, 4 additional individuals required invasive ventilatory support after receiving between 13 and 18 months of Myozyme treatment; 2 of these 4 individuals died after receiving 14 and 25 months of treatment, and after receiving 11 days and 7.5 months of invasive ventilatory support, respectively. No other deaths have been reported through a median follow-up of 20 months, and all 16 surviving individuals continue to be followed. Survival without invasive ventilatory support was substantially greater in the individuals treated with Myozyme in this study versus the expected poor survival of the historical controls. Eleven of the 18 participants experienced 164 infusion-related reactions (i.e., rash, fever, urticaria, decreased oxygen saturation); ranging from mild to moderate intensity (Kishnani, 2007; Product Information Label, 2014).

Kishnani and colleagues (2009) reported results of an extension study of 16 children who continued to receive either 20 mg/kg or 40 mg/kg of alglucosidase alfa, biweekly, for up to a total of 3 years.[9] Survival rate for 17 of the 18 participants who reached age 24 months was 94.5% (95% CI, 83.9 to 100). The survival rate at age 36 months was 72% (95% CI, 47.9 to 96). Seven participants were censored from the analysis because although they were alive, the children had not reached age 36 months by the completion of the study. In comparison, only 1 of the 61 untreated children in the historic control group survived to longer than 24 months (1.9%: 95% CI, 0-5.5). The Kaplan-Meier invasive ventilation-free survival rates at age 24 months and 36 months were 66.7% (95% CI, 44.9 to 88.4) and 49.4% (95% CI, 26 to 72.8), respectively. The authors noted treatment with alglucosidase alfa resulted in a reduction of death by 95%; risk of invasive ventilation or death by 91%, and risk of any type of ventilation or death by 87%. The investigators also noted there were no differences in the dose-effects on survival or ventilator-free survival observed (Kishnani, 2009).

Strothette and colleagues (2010) reported 12-month results of a European trial in which 44 individuals with LOPD of various stages of severity were treated off-FDA label with alglucosidase alfa (Myozyme).[8] This open-label, multi-center, observational study involved treatment with 20mg/kg of Myozyme every other week. Assessments were performed at baseline and every 3 months for the 12 months of ERT. Assessments included serial measures of arm strength using the Walton Gardner Medwin scale (WGMS), and 4 timed function tests which consisted of a 10-m walk, 4-stair climb, modified Gowers' maneuver (rising by oneself from a supine to standing position), and a 6-min walk test with distance

recorded. Additional measures included manual muscle testing using the Medical Research Council (MRC) grading scale, forced vital capacity (FVC), creatine kinase (CK) levels and 36-Item Short Form (SF-36) assessments. The authors noted that due to the heterogeneity of disease status, not all participants were able to complete all tests. There were significant changes from baseline for the modified Gower's test (7.3 sec versus 6 sec), CK levels (mean decrease 10.5%) and the 6-min walk test (341 ± 149.5 m at baseline; 393 ± 157 m at endpoint; p=0.026) while there were no changes in the other functional measures. Although CK levels decreased significantly, they did not correlate to disease severity or results in functional tests. The investigators noted the open-label trial design without a control group could "Neither prove nor disprove that ERT with alglucosidase alfa (Myozyme) is an effective treatment, but concluded that the results suggested ERT resulted in stabilization of neuromuscular deficits over one year with mild functional improvement."

DEFINITIONS

- Cardiac hypertrophy: An abnormal enlargement of the heart muscle.

- Medical Research Council's scale for grading muscle strength:
  The individual's effort is graded on a scale of 0 to 5:
  - 5 — Muscle contracts normally against full resistance.
  - 4 — Muscle strength is reduced, but muscle contraction can still move joint against resistance.
  - 3 — Muscle strength is further reduced such that the joint can be moved only against gravity with the examiner's resistance completely removed. As an example, the elbow can be moved from full extension to full flexion starting with the arm hanging down at the side.
  - 2 — Muscle can move only if the resistance of gravity is removed. As an example, the elbow can be fully flexed only if the arm is maintained in a horizontal plane.
  - 1 — Only a trace or flicker of movement is seen or felt in the muscle, or fasciculations is observed in the muscle.
  - 0 — No movement is observed.

- Vital capacity: The maximum amount expelled from the lungs after a maximum inspiration.

APPENDIX

N/A

CODING INFORMATION: THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	Description
NA	

HCPCS	Description
J0220	Injection, alglucosidase alfa, not otherwise specified, 10 mg [Myozyme]
J0221	Injection, alglucosidase alfa, (Lumizyme), 10 mg

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