Drug Monograph

Drug Name: **Nexviazyme™ (avalglucosidase alfa-ngpt) vial**
Drug Class: **Respiratory: Enzyme Replacement Therapy for Pompe Disease**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Nexviazyme is available in a single-dose vial containing 100 mg of avalglucosidase alfa-ngpt.
Manufacturer:	Manufactured by: Genzyme Corporation, Cambridge, MA 02142.
Summary of Findings:	The efficacy and safety of Nexviazyme was established in a randomized, double-blind, multinational, multicenter trial comparing Nexviazyme to alglucosidase alfa (N=100) in treatment-naïve patients with late-onset Pompe disease. Patients were randomized to receive 20 mg/kg of Nexviazyme or alglucosidase alfa administered IV once every two weeks for 49 weeks. The trial included an open-label, long-term, follow-up phase of up to 5 years, in which patients in the alglucosidase alfa arm were switched to Nexviazyme treatment. The primary endpoint of the study was the change in forced vital capacity (FVC) (% predicted) in the upright position from baseline to Week 49. At Week 49, the least squares (LS) mean change in FVC (% predicted) for patients treated with Nexviazyme and alglucosidase alfa was 2.9% and 0.5% respectively. The estimated treatment difference was 2.4% (95% CI: -0.1, 5.0) favoring Nexviazyme. The most frequently reported adverse reactions (>5%) were headache, diarrhea, nausea, fatigue, arthralgia, myalgia, dizziness, rash, vomiting, pyrexia, abdominal pain, pruritus, erythema, chills, cough, urticaria, dyspnea, hypertension, and hypotension.
Status Recommendation:	☒ Clinical Edit ☐ PA Required ☐ Open Access ☐ PDL
Type of PA Criteria:	☒ Appropriate Indications ☐ Non-Preferred ☐ No PA Required ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

Pompe disease is a rare, genetic, lysosomal storage disease caused by a deficiency of the enzyme acid alpha-glucosidase (GAA), resulting in the buildup of glycogen in cell lysosomes mainly in the liver, heart, and muscles, causing serious and often life-threatening muscle damage and weakness. The incidence of Pompe disease is approximately 1 in 40,000 individuals in the United States. Pompe disease is further classified by the following types: infantile-onset (IOPD) and late-onset (LOPD). Infantile-onset Pompe disease is the result of complete or near complete deficiency of GAA. Late-onset Pompe disease is the result of a partial deficiency of GAA. Some states are now adding GAA deficiency to their newborn screening protocols.
LOPD refers to all cases in which hypertrophic cardiomyopathy (HCM) did not manifest or was not diagnosed at or under the age of 1 year, as well as to all cases with symptom onset above the age of 1 year. The American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) released a consensus statement for the treatment of late-onset Pompe disease in 2012.
Initiation of Enzyme Replacement Therapy (ERT) is recommended at symptom onset and/or onset of detectable proximal muscle weakness or reduced forced vital capacity (FVC) in either upright or supine position. After 1 year of ERT, the patient's condition should be reevaluated to determine whether ERT should be continued. There are no currently published consensus statements and/or guidelines preferring one ERT over another in late-onset Pompe disease.

Dosage Form [3]

Nexviazyme is available in a single-dose vial containing 100 mg of avalglucosidase alfa-ngpt.

Manufacturer [3]

Manufactured by: Genzyme Corporation, Cambridge, MA 02142.

Indication(s) [3]

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

Clinical Efficacy [3,4,5] (mechanism of action/pharmacology, comparative efficacy)

Nexviazyme provides an exogenous source of GAA. The mannose-6-phosphate (M6P) on the avalglucosidase alfa-ngpt molecule mediates binding to M6P receptors on the cell surface with high affinity. After binding, it is internalized and transported into lysosomes where it undergoes proteolytic cleavage that results in increased GAA enzymatic activity. Nexviazyme then exerts enzymatic activity in cleaving glycogen.

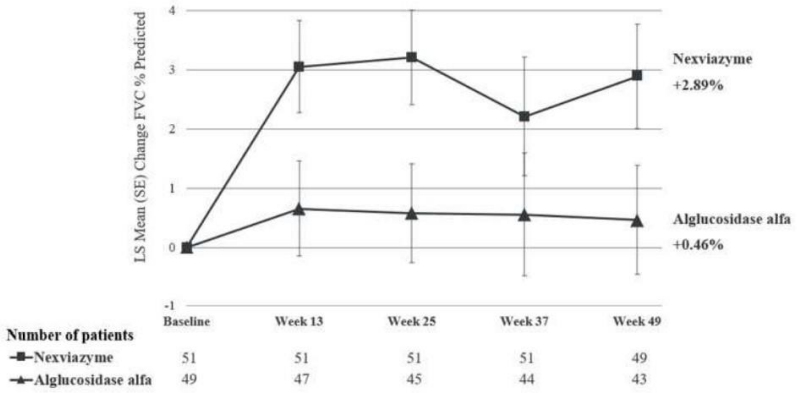
Pharmacokinetics:

Absorption	N/A
Metabolism	Not yet characterized
Excretion	N/A
Half-life	1.6 hours

Clinical Trials Experience

STUDY 1 DESIGN (COMET) **NCT02782741**	Randomized, double-blind, multinational, multicenter trial (N=100)
INCLUSION CRITERIA	• Confirmed GAA enzyme deficiency from any tissue source and/or 2 confirmed GAA gene mutations • Age ≥3 years (i.e., LOPD)
EXCLUSION CRITERIA	• Participant has known Pompe specific cardiac hypertrophy • Participant is wheelchair dependent • Participant is not able to ambulate 40 meters without stopping and without and assistive device • Participant requires invasive-ventilation • Participant is not able to successfully perform repeated FVC measurements in an upright position of ≥30% predicted and ≤85% predicted • Participant has had previous treatment with alglucosidase alfa or any investigational therapy for Pompe disease • Participant has prior or current use of immune tolerance induction therapy
TREATMENT REGIMEN	• Patients were randomized in a 1:1 ratio based on baseline FVC, gender, age, and country to receive 20 mg/kg of Nexviazyme or alglucosidase alfa administered intravenously once every two weeks for 49 weeks. • The trial included an open-label, long-term, follow-up phase of up to 5 years, in which patients in the alglucosidase alfa arm were switched to Nexviazyme treatment.
RESULTS	The primary endpoint of Study 1 was the change in FVC (% predicted) in the upright position from baseline to week 49. **Summary Results of FVC (% predicted) in Upright Position in Treatment-Naive Patients with LOPD (Study 1)*** **Nexviazyme (N=51)** / **Alglucosidase Alfa (N=49)** **Pretreatment baseline** — Mean (SD) — 62.5 (14.4) / 61.6 (12.4) **Week 49** — Mean (SD) — 65.5 (17.4) / 61.2 (13.5) **Estimated change from baseline to week 49** — LS mean (SE) — 2.9[†] (0.9) / 0.5[†] (0.9) **Estimated difference between groups in change from baseline to week 49** — LS mean (95% CI) — 2.4[†‡] (-0.1, 5.0) SD: standard deviation, SE: standard errors, LS: least squares means, CI: confidence interval *All randomized patients [†]Estimated using a mixed model for repeated measures (MMRM) including baseline FVC (% predicted, as continuous), sex, baseline age (years), treatment group, visit, and treatment-by-visit interaction term as fixed effects. [‡]Noninferiority margin of 1.1% (p=0.0074). Statistical superiority of Nexviazyme over alglucosidase alfa was not achieved (p=0.06).

Figure 1: Plot of LS Mean (SE) Change from Baseline of FVC (% predicted) in Upright Position over Time in Treatment-Naive Patients with LOPD (Study 1)*



*All randomized patients

- At week 49, the least squares (LS) mean change in FVC (% predicted) for patients treated with Nexviazyme and alglucosidase alfa was 2.9% and 0.5%, respectively. The estimated treatment difference was 2.4% (95% CI: -0.1, 5.0) favoring Nexviazyme.
- The key secondary endpoint of Study 1 was change in total distance walked in 6MWT from baseline to week 49. At week 49, the LS mean change from baseline in 6MWT for patients treated with Nexviazyme and alglucosidase alfa was 32.2 meters and 2.2 meters, respectively. The estimated treatment difference was 30 meters (95% CI: 1.3, 58.7) favoring Nexviazyme.

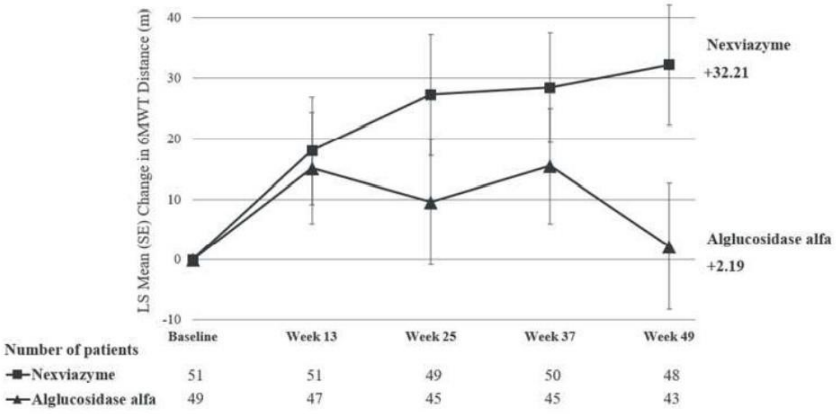
Summary Results of 6MWT in Treatment-Naive Patients with LOPD (Study 1)*

		Nexviazyme (N=51)	Alglucosidase Alfa (N=49)
Pretreatment baseline	Mean (SD)	399.3 (110.9)	378.1 (116.2)
Week 49	Mean (SD)	441.3 (109.8)	383.6 (141.1)
Estimated change from baseline to week 49	LS mean (SE)	32.2Ŧ (9.9)	2.2Ŧ (10.4)
Estimated difference between groups in change from baseline to week 49	LS mean (95% CI)	30.0Ŧŧ (1.3, 58.7)	

*All randomized patients

ŦThe MMRM model for 6MWT distance adjusts for baseline FVC (% predicted), baseline 6MWT (distance walked in meters), baseline age (years), gender, treatment group, visit, and treatment-by-visit interaction as fixed effects.

ŧp-value at normal level, without multiplicity adjustment (p=0.04)

	Figure 2: Plot of LS Mean (SE) Change from Baseline of 6MWT (distance walked, in meters) over Time in Treatment-Naive Patients with LOPD (Study 1)*  Number of patients Nexviazyme 51 51 49 50 48 Alglucosidase alfa 49 47 45 45 43 *All randomized patients
SAFETY	Discussed in the Adverse Effects section below.

Contraindications [3,4]

- None

Warnings and Precautions [3,4]

Black Boxed Warnings:

- **Hypersensitivity Reaction Including Anaphylaxis:** Appropriate medical support measures, including cardiopulmonary resuscitation (CPR) equipment, should be readily available. If a severe hypersensitivity reaction occurs, Nexviazyme should be discontinued immediately and appropriate medical treatment should be initiated.
- **Infusion-Associated Reactions (IARs):** If severe IARs occur, consider immediate discontinuation and initiation of appropriate medical treatment.
- **Risk of Acute Cardiorespiratory Failure in Susceptible Patients:** Patients susceptible to fluid volume overload, or those with acute underlying respiratory illness or compromised cardiac or respiratory function, may be at risk of serious exacerbation of their cardiac or respiratory status during Nexviazyme infusion.

Adverse Effects [3,4]

Most common, ≥6%	Nexviazyme (N=51) n (%)	Alglucosidase Alfa (N=49) n (%)
Headache	11 (22)	16 (33)
Fatigue	9 (18)	7 (14)
Diarrhea	6 (12)	8 (16)
Nausea	6 (12)	7 (14)
Arthralgia	5 (10)	8 (16)
Dizziness	5 (10)	4 (8)
Myalgia	5 (10)	7 (14)
Pruritus	4 (8)	4 (8)

Vomiting	4 (8)	3 (6)
Dyspnea	3 (6)	4 (8)
Erythema	3 (6)	3 (6)
Paresthesia	3 (6)	2 (4)
Urticaria	3 (6)	1 (2)

Drug Interactions [3,4]

- None

Dosage and Administration [3,4]

- Nexviazyme must be reconstituted and diluted prior to use
- Administered as an intravenous infusion (1 mg/kg/hr) based on patient weight:
- ≥30 kg, the recommended dosage is 20 mg/kg (of actual body weight) every two weeks
- <30 kg, the recommended dosage is 40 mg/kg (of actual body weight) every two weeks

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/Year
Avalglucosidase alfa	Nexviazyme™	Genzyme	≥30 kg patient: 20 mg/kg (of actual body weight) every two weeks; <30 kg patient: 40 mg/kg (of actual body weight) every two weeks	40 mg/kg (25 kg patient): $445,874; 20 mg/kg (70 kg patient): $624,224
Alglucosidase alfa	Lumizyme®	Genzyme	20 mg/kg/dose IV given over 4 hours every two weeks	$624,224 (70 kg patient)

** Wholesale Acquisition Cost

Conclusion

Nexviazyme provides an exogenous source of GAA for patients 1 year of age and older with late-onset Pompe disease. The efficacy and safety of Nexviazyme was established in a randomized, double-blind, multinational, multicenter trial comparing Nexviazyme to alglucosidase alfa (N=100) in treatment-naïve patients with late-onset Pompe disease. Patients were randomized to receive 20 mg/kg of Nexviazyme or alglucosidase alfa administered IV once every two weeks for 49 weeks. At Week 49, the least squares (LS) mean change in FVC (% predicted) for patients treated with Nexviazyme and alglucosidase alfa was 2.9% and 0.5% respectively. The estimated treatment difference was 2.4% (95% CI: -0.1, 5.0) favoring Nexviazyme. The most common adverse reactions were headache, diarrhea, nausea, fatigue, arthralgia, myalgia, dizziness, rash, vomiting, pyrexia, abdominal pain, pruritus, erythema, chills, cough, urticaria, dyspnea, hypertension, and hypotension.

Recommendation

The MO Healthnet Division recommends including this drug in the Pompe Disease clinical edit.

References

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7) Culper E, Berger K, Leshner R, et al. Consensus Treatment Recommendations for Late-Onset Pompe Disease. *Muscle Nerve* 45:319-333, 2012.
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