NEW DRUG APPROVAL

Brand Name	Nexviazyme™
Generic Name	avalglucosidase alfa-ngpt
Drug Manufacturer	Genzyme Corporation

New Drug Approval

FDA Approval Date: August 06, 2021

Review Designation: Orphan

Type of Review: Biologic License Application (BLA): 761194

Dispensing restrictions: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Pompe disease is a rare (estimated at 1 in every 40,000 births), inherited and often fatal disorder that disables the heart and skeletal muscles. It is caused by mutations in a gene that makes an enzyme called acid alpha-glucosidase (GAA).

Pompe disease affects an estimated 3,500 people in the United States and can present as infantile-onset Pompe disease (IOPD), the most severe form of Pompe disease with rapid onset in infancy, and late-onset Pompe disease (LOPD), which progressively damages muscles over time. LOPD symptoms may present at any age. However, due to the wide spectrum of clinical presentations and progressive nature of the disease, it can take seven to nine years before patients receive an accurate diagnosis. As the disease progresses, people with LOPD may require mechanical ventilation to help with breathing or a wheelchair to assist with mobility.

Efficacy

Study 1 (NCT02782741) was a randomized, double-blinded, multinational, multicenter trial comparing the efficacy and safety of Nexviazyme™ to alglucosidase alfa in 100 treatment-naive patients with LOPD. Patients were randomized in a 1:1 ratio based on baseline forced vital capacity (FVC), gender, age, and country to receive 20 mg/kg of Nexviazyme™ or alglucosidase alfa administered intravenously once every two weeks for 49 weeks.

Endpoints and Results from the 49-Week Active-Controlled Period in Study 1 was the change in FVC (% predicted) in the upright position from baseline to Week 49. At Week 49, the least squares (LS) mean change in FVC (% predicted) for patients treated with Nexviazyme™ and alglucosidase alfa was 2.9% and 0.5%, respectively. The estimated treatment difference was 2.4% (95% CI: -0.1, 5.0) favoring Nexviazyme™.

Table: 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)	

*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).

The key secondary endpoint of Study 1 was change in total distance walked in 6 minutes (6-Minute Walk Test, 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™.

Table: Summary Results of 6-Minute Walk Test in Treatment-Naive Patients with LOPD (Study 1 continued)

		NEXVIAZYME (n=51)	Alglucosidase Alfa (n=49)
Week 49	Mean (SD)	441.3 (109.8)	383.6 (141.1)
Estimated change from baseline to week 49	LS mean (SE)	32.2† (9.9)	2.2† (10.4)
Estimated difference between groups in change from baseline to week 49	LS mean (95% CI)	30.0†‡ (1.3, 58.7)	

*All randomized patients
†The 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.
‡p-value at nominal level, without multiplicity adjustment (p=0.04).

Safety

ADVERSE EVENTS

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

WARNINGS & PRECAUTIONS

Hypersensitivity Reactions Including Anaphylaxis: Prior to Nexviazyme™ administration, consider pretreating with antihistamines, antipyretics, and/or corticosteroids. Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available during Nexviazyme™ administration.

- If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, Nexviazyme™ should be discontinued immediately and appropriate medical treatment should be initiated.
- If a mild or moderate hypersensitivity reaction occurs, the infusion rate may be slowed or temporarily stopped.

Infusion-Associated Reactions: Antihistamines, antipyretics, and/or corticosteroids can be given prior to Nexviazyme™ administration to reduce the risk of infusion-associated reactions (IARs). However, IARs may still occur in patients after receiving pretreatment. If severe IARs occur, consider immediate discontinuation of

Nexviazyme™, initiation of appropriate medical treatment, and the benefits and risks of readministering Nexviazyme™ following severe IARs.

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 for whom fluid restriction is indicated may be at risk of serious exacerbation of their cardiac or respiratory status during the Nexviazyme™ infusion. More frequent monitoring of vitals should be performed during Nexviazyme™ infusion in these patients. Some patients may require prolonged observation times.

CONTRAINDICATIONS

None.

Clinical Pharmacology

MECHANISMS OF ACTION

Pompe disease (also known as glycogen storage disease type II, acid maltase deficiency, and glycogenosis type II) is an inherited disorder of glycogen metabolism caused by a deficiency of the lysosomal enzyme acid α-glucosidase (GAA), which results in intralysosomal accumulation of glycogen in various tissues.

Avalglucosidase alfa-ngpt provides an exogenous source of GAA. The M6P on avalglucosidase alfa-ngpt 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. Avalglucosidase alfa-ngpt then exerts enzymatic activity in cleaving glycogen.

Dose & Administration

ADULTS

- Consider administering antihistamines, antipyretics, and/or corticosteroids prior to Nexviazyme™ administration to reduce the risk of IARs.
- Must be reconstituted and diluted prior to use.
- Nexviazyme™ is administered as intravenous infusion. For patients weighing:
  ≥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

PEDIATRICS

Refer to adult dosing.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

N/A

HEPATIC IMPAIRMENT

N/A

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

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