# New Drug Fact Blast

## Clinical Services

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| **Drug/Manufacturer:** | **Nexviazyme™ (avalglucosidase alfa-ngpt) [Sanofi Genzyme]** |
| **Dosage Formulations:** | 100 mg of avalglucosidase alfa-ngpt as a lyophilized powder in a single-dose vial for reconstitution |
| **FDA Approval Date:**<br>**FDB File Date:** | FDA: August 6, 2021<br>FDB: August 15, 2021 |
| **Indication:** | Treatment of patients 1 year of age and older with late-onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency) |
| **Mechanism of Action:** | Avalglucosidase alfa-ngpt provides an exogenous source of GAA. The mannose-6-phosphate (M6P) receptor 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:** | • Nexviazyme must be reconstituted and diluted prior to use<br>• Administered as an intravenous infusion based on body weight. The recommended starting infusion rate is 1mg/kg/hour. If there are no signs of infusion-associated reactions (IAR), gradually increase the infusion rate every 30 minutes in each of the following steps: 3mg/kg/hour, 5mg/kg/hour, then 7mg/kg/hour. The approximate total infusion duration is 4 to 5 hours.<br>• ≥30 kg, the recommended dosage is 20 mg/kg (of actual body weight) every two weeks<br>• <30 kg, the recommended dosage is 40 mg/kg (of actual body weight) every two weeks |
| **Disease State Clinical Highlights:** | • 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.<br>• The incidence of Pompe disease is approximately 1 in 40,000 individuals in the United States.<br>• Pompe disease is further classified by the following types: infantile-onset (IOPD) and late-onset (LOPD).<br>• 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.<br>• Some states are now adding GAA deficiency to their newborn screening protocols.<br>• 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.<br>• The American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) released a consensus statement for the treatment of late-onset Pompe disease in 2012.<br>  ○ 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.<br>  ○ After 1 year of ERT, the patient's condition should be reevaluated to determine whether ERT should be continued.<br>• There are no currently published consensus statements and/or guidelines preferring one ERT over another in late-onset Pompe disease. |

**Drug Clinical Highlights:**

- Nexviazyme specifically targets the M6P receptor, the key pathway for enzyme replacement therapy, to effectively clear glycogen build-up in muscle cells.
- Nexviazyme was designed with a 15-fold increase in M6P content compared to Lumizyme® (alglucosidase alfa), which is intended to increase cellular uptake of the exogenous enzyme. However, the clinical implications of this altered M6P content have not been established in clinical trials.
- **Black Boxed Warning**: Hypersensitivity reactions including anaphylaxis, Infusion-Associated Reactions (IARs) and risk of acute cardiorespiratory failure in susceptible patients.
- Consider administering antihistamines, antipyretics, and/or corticosteroids prior to Nexviazyme administration to reduce the risk of IARs.
- Dosage modifications are suggested if hypersensitivity reactions or IARs occur.

- **Study 1 (NCT02782741/COMET)** 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 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.
- Of the 100 randomized patients, 52 were males, the baseline median age was 49 years old (range from 16 to 78 years), median baseline weight was 76.4 kg (range from 38 to 139 kg), median length of time since diagnosis was 6.9 months (range from 0.3 to 328.4 months), mean age at diagnosis was 46.4 years old (range from 11 to 78 years), mean FVC (% predicted) at baseline was 62.1% (range from 32 to 85%), and mean 6 minute walk test (6MWT) at baseline was 388.9 meters (range from 118 to 630 meters).
- The primary endpoint of 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 (see Table 1).

**Table 1: 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[Ŧ] (0.9) | 0.5[Ŧ] (0.9) |
| **Estimated difference between groups in change from baseline to week 49** | LS mean (95% CI) | 2.4[Ŧt] (-0.1, 5.0) | |

SD: standard deviation, SE: standard errors, LS: least squares means, CI: confidence interval

*All randomized patients

[Ŧ]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.

[t]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 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 2: 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) | 32.2 ǂ (9.9) | 2.2 ǂ (10.4) |
| **Estimated difference between groups in change from baseline to week 49** | LS mean (95% CI) | 30.0 ǂǂ (1.3, 58.7) | |

*All randomized patients
ǂThe 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.
ǂp-value at normal level, without multiplicity adjustment (p=0.04)

**Safety Data:**

- During the double-blind active-controlled period of 49 weeks, serious adverse reactions were reported in 1 (2%) patient treated with Nexviazyme and in 3 (6%) patients treated with alglucosidase alfa. The most frequently reported (> 5%) adverse reactions in Nexviazyme-treated patients were headache, fatigue, diarrhea, nausea, arthralgia, dizziness, myalgia, pruritus, vomiting, dyspnea, erythema, paresthesia, and urticaria.
- Table 3 summarizes the adverse reactions that occurred in at least 3 Nexviazyme-treated patients (≥ 6%) in Study 1. Study 1 was not designed to demonstrate a statistically significant difference in the incidence of adverse reactions between the Nexviazyme and the alglucosidase alfa treatment groups.

**Table 3: Adverse Reactions Reported in at Least 6% of Nexviazyme-Treated Patients with LOPD in Study 1**

| Adverse Reaction | Nexviazyme (N=51) n(%) | Alglucosidase Alfa (N=49) n(%) |
|---|---|---|
| Headache | 11 (22%) | 16 (33%) |
| Fatigue | 9 (18%) | 7 (14%) |
| Diarrhea | 6 (12%) | 8 (15%) |
| 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%) |

**Price Per Unit (WAC):** Weight-based dosing, 70 kg patient ($1,714.90/vial): $624,223.60 estimated annual WAC cost

**Therapeutic Alternatives:**

- Myozyme® was the first ERT approved by the FDA in 2006 for early-onset disease but it is no longer marketed in the United States.
- Currently, there are two FDA-approved ERTs for late-onset Pompe disease: Lumizyme® and now Nexviazyme™. Both therapies are manufactured by Sanofi Genzyme.
- Lumizyme and Nexviazyme both work by replacing the deficient GAA, thereby reducing the accumulated glycogen in heart and skeletal muscle cells and the manifestations of the disease.
- Lumizyme is indicated in IOPD and LOPD. Nexviazyme is only indicated in LOPD.
- COMET study data showed meaningful improvements through week 49 in respiratory muscle function and mobility in patients treated with avalglucosidase alfa, demonstrating comparable efficacy to Lumizyme treatment. Safety profile, improvements in lower extremity muscle strength, and quality of life were also similar between the therapies.
- Sanofi Genzyme has stated they will price Nexviazyme at parity with Lumizyme. However, for patients requiring higher dosing (40 mg/kg), Nexviazyme would be double the cost of Lumizyme.

**Table 4. Nexviazyme and Lumizyme**

| | Nexviazyme | Lumizyme |
|---|---|---|
| Manufacturer | Sanofi Genzyme | Sanofi Genzyme |
| FDA Approval Date | August 6, 2021 | May 24, 2010 |
| Indication | LOPD | IOPD and LOPD |
| Dosing | • Patient weight ≥ 30 kg, 20 mg/kg (actual body weight) IV (1 mg/kg/hour) every two weeks<br><br>• Patient weight < 30 kg, 40 mg/kg (actual body weight) IV (1 mg/kg/hour) every two weeks | • 20 mg/kg IV over 4 hours every 2 weeks |
| Black Boxed Warning | • Hypersensitivity reactions including anaphylaxis<br>• Infusion-Associated Reactions (IARs)<br>• Risk of acute cardiorespiratory failure in susceptible patients | • Life-threatening anaphylactic reactions, severe allergic reactions, and immune-mediated reactions |
| WAC Estimated Annual Pricing | 40 mg/kg (25 kg patient): $445,874.00<br><br>20 mg/kg (70 kg patient): $624,223.60 | 20 mg/kg (25 kg patient): $222,937.00<br><br>20 mg/kg (70 kg patient): $624,223.60 |

**Prior Authorization Approval Criteria:**

**Must meet the following criteria:**

Initial Therapy:

- Prescribed by or in consultation with a neurologist, geneticist, or other specialist in the treated disease state **AND**
- Participant aged ≥ 1 years **AND**
- Documented diagnosis of Pompe disease (ICD10 E74.02) **AND**
- Diagnosis of late-onset Pompe disease (LOPD), as evidenced by the following:
  - Enzyme assay showing a deficiency of acid alpha-glucosidase (GAA) activity in the blood, skin, or muscle
  - Genetic testing showing a pathogenic variant of the GAA gene **AND**

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| | • Patient has measurable signs of Pompe disease, such as impairment in pulmonary function or motor weakness **AND**<br>• Documentation of baseline percent-predicted forced vital capacity (FVC) and 6-minute walk test (6MWT)<br>• Approval for one year<br><br><u>Coverage will not be provided in the following circumstances:</u><br>• Concomitant use of alglucosidase alfa (Lumizyme)<br><br><u>Continuation of Therapy:</u><br>• Documentation of response to therapy, as evidenced by an improvement or stabilization in percent-predicted FVC and/or 6MWT<br><br>**Additional Provider Diagnostic/Monitoring Criteria, if desired:**<br>• 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. For these patients, more frequent monitoring of vitals should be performed during infusion. |
| **Implication to State Medicaid Program:** | **LOE: Patent expiration data unavailable at this time.**<br><br>• Sanofi registered the Phase 3 Baby-COMET clinical trial (NCT04910776) evaluating Nexviazyme in the IOPD population, in participants ≤ 6 months of age. This is a single group, treatment, Phase 3, open-label study. The primary outcome of this study is the proportion of participants who are alive and free of invasive ventilation at week 52. The trial is recruiting patients, with an estimated start date of August 31, 2021, and an estimated primary completion date of May 2024.<br>• Amicus' product AT-GAA (cipaglucosidase alfa/miglustat) is a recombinant human acid alpha-glucosidase (rhGAA) enzyme with an optimized carbohydrate structure (ATB20) and miglustat (enzyme inhibitor) currently being studied in LOPD. In the Phase 3 PROPEL study (NCT03729362) of AT-GAA, the primary endpoint of change from baseline to week 52 on the 6MWT was not statistically significant compared to the Lumizyme arm. AT-GAA did slow the rate of respiratory deterioration versus Lumizyme, and the results were statistically significant. Despite these conflicting trial results, Amicus has stated that it is continuing to pursue FDA approval. In August 2021, Amicus announced that the nonclinical and final clinical components were submitted. |

**References:**


1. Nexviazyme [package insert]. Cambridge, MA: Sanofi Genzyme Corporation; 2021.
2. Lumizyme [package insert]. Cambridge, MA: Sanofi Genzyme Corporation; 2010.
3. IPD Analytics. Endocrinology and Metabolic Agents: Pompe Disease. August 2021.
4. IPD Analytics. New Drug Review: Nexviazyme (avalglucosidase alfa-ngpt). August 2021.
5. "FDA approves Nexviazyme (avalglucosidase alfa-ngpt), an important new treatment option for late-onset Pompe disease." Sanofi Press Release. Available online: https://www.globenewswire.com/news-release/2021/08/06/2276588/0/en/FDA-approves-Nexviazyme-avalglucosidase-alfa-ngpt-an-important-new-treatment-option-for-late-onset-Pompe-disease.html. Accessed August 2021.
6. "FDA approved Sanofi Genzyme's Nexviazyme for treatment of Pompe disease. "Muscular Dystrophy Association. Available online: https://strongly.mda.org/fda-approves-sanofi-genzymes-nexviazyme-for-treatment-of-pompe-disease/. Accessed August 2021.
7. Culper E, Berger K, Leshner R, et al. Consensus Treatment Recommendations for Late-Onset Pompe Disease. *Muscle Nerve* 45:319-333, 2012.
8. Pompe Disease. National Organization for Rare Disorders. Available online: https://rarediseases.org/rare-diseases/pompe-disease/. Accessed: August 2021.