For the use only of a Registered Medical Practitioner or a Hospital or Laboratory
This package insert is continually updated: Please read carefully before using a new pack.
WARNING: To be sold by retail on the prescription of a specialist in Medicine only

Avalglucosidase Alfa Powder for concentrate for solution for infusion

NEXVIAZYME®

1. Generic Name: Avalglucosidase Alfa

2. Qualitative and quantitative composition:

Each 100 mg vial contains: Active ingredient- Avalglucosidase alfa IH 100 mg. Excipients - L-Histidine HCl monohydrate JP/Ph. Eur. 6.5 mg, L-Histidine USP-NF /JP/Ph. Eur 10.7 mg, Glycine USPNF/ JP/Ph. Eur 200 mg Mannitol USP-NF /JP/Ph. Eur 200mg, Polysorbate 80 Ph. Eur /NF/JP1.0 mg.

The powder for injection is reconstituted with nominal 10 mL sterile WFI. Following reconstitution, each vial contains 10.3 mL reconstituted solution and a total extractable volume of 10.0 mL at 10 mg/mL of Nexviazyme. Each vial contains an overfill to compensate for liquid loss during preparation. This overfill ensures that, after dilution with the entire content, there is solution containing 10 mg/mL of Nexviazyme.

Nexviazyme is Recombinant human acid α-glucosidase conjugated with synthetic bis-mannose-6-phosphate (bis-M6P).

3. Dosage Form and Strengths: Nexviazyme®, 100 mg/vial. Each vial contains 10 mg/mL avalglucosidase alfa after reconstitution with sterile water for injection (WFI) (100 mg extractable dose. Nexviazyme is available as Sterile lyophilized powder administered by intravenous (IV) infusion and Powder for concentrate for solution for infusion.

4. Clinical Particulars

4.1 Therapeutic indication: Nexviazyme® (avalglucosidase alfa) is indicated for the treatment of long-term enzyme replacement therapy for the treatment of patients with Pompe disease (acid α-glucosidase deficiency).

4.2 Posology and Administration:

Patients with late-onset Pompe disease (LOPD)
The recommended dose of Nexviazyme is 20 mg/kg of body weight administered once every 2 weeks.

Patients with infantile-onset Pompe disease (IOPD)
For IOPD patients who experience lack of improvement or insufficient response in cardiac, respiratory, and/or motor function while receiving 20 mg/kg, a dose increases to 40 mg/kg every other week should be considered in the absence of safety concerns (e.g., severe hypersensitivity, anaphylactic reactions, or risk of fluid overload). In patients who do not tolerate avalglucosidase alfa at 40 mg/kg every other week (e.g., severe hypersensitivity, anaphylactic reactions, or risk of fluid overload), consider decreasing the dose to 20 mg/kg every other week.

4.3 Contraindications:
Life-threatening hypersensitivity to the active substance or to any of the excipients when re-challenge was unsuccessful.

4.4 Special Warnings and Precautions for use:

HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS

Hypersensitivity reactions, including anaphylaxis, have been reported in Nexviazyme-treated patients. In clinical studies 60 (43.5%) patients experienced hypersensitivity reactions including 6 patients who reported severe hypersensitivity reactions and 2 patients who experienced anaphylaxis. Some of the hypersensitivity reactions were IgE mediated. Anaphylaxis symptoms included respiratory distress, chest pressure, generalized flushing, cough, dizziness, nausea, redness on palms, swollen lower lip, decreased breath sounds, redness on feet, swollen tongue, itchy palms and feet, and oxygen desaturation. Symptoms of severe hypersensitivity reactions included respiratory failure, respiratory distress, and rash.

Appropriate medical support measures, including cardiopulmonary resuscitation equipment especially for patients with cardiac hypertrophy and patients with significantly compromised respiratory function, should be readily available when Nexviazyme is administered.

If severe hypersensitivity or anaphylaxis occur, Nexviazyme should be discontinued immediately, and appropriate medical treatment should be initiated. The risks and benefits of re-administering Nexviazyme following anaphylaxis or severe hypersensitivity reaction should be considered. Some patients have been re-challenged using slower infusion rates at a dose lower than the recommended dose. In patients with severe hypersensitivity, desensitization procedure to Nexviazyme may be considered. If the decision is made to re-administer the product, extreme caution should be exercised, with appropriate resuscitation measures available. Once a patient tolerates the infusion, the dose may be increased to reach the approved dose.

If mild or moderate hypersensitivity reactions occur, the infusion rate may be slowed or temporarily stopped.

INFUSION-ASSOCIATED REACTIONS

In clinical studies, IARs were reported to occur at any time during and/or within a few hours after the infusion of Nexviazyme and were more likely with higher infusion rates. IARs were reported in approximately 42 (30.4%) patients treated with Nexviazyme in clinical studies.[2]The majority of IARs were assessed as mild to moderate and included symptoms such as chills, cough, diarrhea, erythema, fatigue, headache, influenza like illness, nausea, ocular hyperemia, pain in extremity, pruritus, rash, rash erythematous, tachycardia, urticaria, vomiting, chest discomfort, dizziness, hyperhidrosis, lip swelling, oxygen saturation decreased, pain, palmar erythema, swollen tongue and tremor. In clinical studies, 3 (2.2%) patients reported severe IARs including symptoms of chest discomfort, nausea and increased blood pressure.

Patients with an acute underlying illness at the time of Nexviazyme infusion appear to be at greater risk for IARs. Patients with advanced Pompe disease may have compromised cardiac and respiratory function, which may predispose them to a higher risk of severe complications from IARs.
Antihistamines, antipyretics, and/or corticosteroids can be given to prevent or reduce IARs. However, IARs may still occur in patients after receiving pretreatment.

If severe IARs occur, immediate discontinuation of the administration of Nexviazyme should be considered and appropriate medical treatment should be initiated. The benefits and risks of re-administering Nexviazyme following severe IARs should be considered. Some patients have been re-challenged using slower infusion rates at a dose lower than the recommended dose. Once a patient tolerates the infusion, the dose may be increased to reach the approved dose. If a mild or moderate IARs occur regardless of pre-treatment, decreasing the infusion rate or temporarily stopping the infusion may ameliorate the symptoms.

IMMUNOGENICITY

Treatment emergent anti-drug antibodies (ADA) were reported in both treatment naïve (95%) and treatment experienced patients (49%) (refer adverse reaction section).

IARs and hypersensitivity reactions may occur independent of the development of ADA. The majority of IARs and hypersensitivity reactions were mild or moderate and were managed with standard clinical practices. In treatment-naïve patients, a trend for increases in the incidence of IARs was observed with increasing ADA titers, with the highest incidence of IARs (61.5%) reported in the high ADA peak titer range ≥12,800, compared with an incidence of 24.1% in patients with intermediate ADA titer 1,600-6,400, an incidence of 7.1% in those with low ADA titer 100-800 and an incidence of 33.3% in those who were ADA negative. In clinical studies, the development of ADA did not impact clinical efficacy (refer adverse reaction section).
ADA testing may be considered if patients do not respond to therapy. Adverse-event-driven immunologic testing, including IgG and IgE ADA, may be considered for patients who have risk for allergic reaction or previous anaphylactic reaction to Alglucosidase alfa.

RISK OF ACUTE CARDIORESPIRATORY FAILURE

Caution should be exercised when administering Nexviazyme to patients susceptible to fluid volume overload or patients with acute underlying respiratory illness or compromised cardiac and/or respiratory function for whom fluid restriction is indicated. These patients may be at risk of serious exacerbation of their cardiac or respiratory status during infusion. Appropriate medical support and monitoring measures should be readily available during Nexviazyme infusion, and some patients may require prolonged observation times that should be based on the individual needs of the patient.

CARDIAC ARRHYTHMIA AND SUDDEN 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 or for other surgical procedures in patients with IOPD with cardiac hypertrophy.
Cardiac arrhythmia, including ventricular fibrillation, ventricular tachycardia, and bradycardia, resulting in cardiac arrest or death, or requiring cardiac resuscitation or defibrillation, have been associated with the use of general anesthesia in IOPD patients with cardiac hypertrophy.

4.5 Drug Interactions

DRUG/DRUG

No drug interaction studies have been conducted with Nexviazyme.

DRUG/FOOD

No drug interaction studies have been conducted with Nexviazyme.

PHARMACEUTICAL INCOMPATIBILITIES

In the absence of compatibility studies, Nexviazyme should not be mixed with other medicinal products.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

PREGNANCY

There are no available data on the use of Nexviazyme in pregnant women. No conclusions can be drawn regarding whether or not Nexviazyme is safe for use during pregnancy.

Nexviazyme should be used during pregnancy only if the potential benefits to the mother outweigh the potential risks, including those to the fetus.

Most reproductive toxicity studies in mice included the pretreatment with diphenhydramine (DPH) to prevent or minimize hypersensitivity reactions. The effects of Nexviazyme were evaluated based on comparison with a control group treated with DPH alone. Rabbits tested in reproductive toxicity studies

were not pretreated with DPH because hypersensitivity reactions were not observed.

Embryo-fetal toxicity studies performed in pregnant mice at doses of 0, 10, 20, or 50 mg/kg/day administered intravenously once daily on Gestational Days 6 through 15 resulted in an immunologic response, including an anaphylactoid response, in some dams at the highest dose of 50 mg/kg/day (17 times the human steady-state area under the curve (AUC) at the recommended biweekly dose of 20 mg/kg for patients with LOPD). Increased post implantation loss and mean number of late resorptions were observed in this group. No effects were seen at 20 mg/kg/day (4.8 times the human steady-state AUC at the recommended biweekly dose of 20 mg/kg for patients with LOPD). Placental transfer studies determined that avalglucosidase alfa is not transported from the maternal to the fetal circulation in mice, suggesting that the embryo-fetal effects were due to maternal toxicity relating to the immunologic response. The maternal no observed adverse effect level (NOAEL) was 50 mg/kg/day IV (AUC_{0-24} = 2080 µg·h/mL) and the developmental NOAEL was 20 mg/kg/day IV (AUC_{0-24} = 582 µg·h/mL) (refer non-clinical section).

Embryo-fetal toxicity studies performed in rabbits at doses of 0, 30, 60, and 100 mg/kg/day administered intravenously once daily on Gestational Days 6 through 19 resulted in no adverse effects in the fetuses at the highest dose (100 mg/kg/day; 91 times the human steady-state AUC at the recommended biweekly dose of 20 mg/kg for patients with LOPD). Furthermore, the administration of Nexviazyme intravenously every other day in mice from Gestational Day 6 through Postpartum Day (PPD) 20 did not produce adverse effects in the offspring at the highest dose of 50 mg/kg (maternal exposure not evaluated) (refer non-clinical section).

LACTATION

There are no available data on the presence of Nexviazyme in human milk or the effects of Nexviazyme on milk production or the breastfed infant. No conclusions can be drawn regarding whether or not Nexviazyme is safe for use during breastfeeding. Nexviazyme should be used during breastfeeding only if the potential benefits to the mother outweigh the potential risks, including those to the breastfed child (refer non-clinical section).

PEDIATRIC PATIENTS

The safety and efficacy of Nexviazyme have been established in pediatric patients older than 6 months with Pompe disease. There are no data available in patients 6 months of age and younger. The safety and efficacy of avalglucosidase alfa were assessed in 19 patients with IOPD (1 to 12 years of age) and 1 pediatric patient with LOPD (16 years of age) in 2 different clinical studies (refer clinical section).

GERIATRIC PATIENTS

Clinical studies with Nexvaizyme included 14 patients aged 65-74 years and 3 patients 75 years of age and older. There is no recommended dose adjustment for patients over the age of 65 (refer clinical section).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Because dizziness, hypotension, and fatigue have been reported as IARs, this may affect the ability to drive and use machines on the day of the infusion. (Refer to adverse reaction section).

4.8 Undesirable effects

The pooled safety analysis from 4 clinical studies (EFC14028/COMET, ACT14132/mini-COMET, TDR12857/NEO, and LTS13769/NEO-EXT) included a total of 138 patients (118 adult and 20 pediatric patients) treated with Nexviazyme.

Serious adverse reactions reported in patients treated with Nexviazyme were headache, dyspnea, respiratory distress, nausea, skin discoloration, chills, chest discomfort, pyrexia, blood pressure increased, body temperature increased, heart rate increase, and oxygen saturation decreased.

A total of 2 patients receiving Nexviazyme in clinical studies permanently discontinued treatment, of this 1 patient discontinued the treatment because of serious adverse event.

The most frequently reported adverse drug reactions (ADRs) (>5%) were headache, nausea, pruritus, rash, urticaria, fatigue and chills.

IARs were reported in 42 (30.4%) patients. IARs reported in more than one patient included chills, cough, diarrhea, erythema, fatigue, headache, influenza-like illness, nausea, ocular hyperemia, pain in extremity, pruritus, rash, rash erythematous, tachycardia, urticaria, vomiting, chest discomfort, dizziness, hyperhidrosis, lip swelling, oxygen saturation decreased, pain, palmar erythema, swollen tongue and tremor.The majority of IARs were assessed as mild to moderate (refer warning/precautions section).

ADRs reported in at least 2 patients (≥1%) treated with Nexviazyme in the pooled analysis of clinical studies are listed in Table 1.

Table 1 - Adverse reactions occurring in at least 2 patients (≥ 1%) treated with Nexviazyme in pooled analysis of clinical studies

System Organ Class	Frequency	<Nexviazyme> patients (N = 138)	
		Preferred Term	Number of patients n (%)
Nervous system disorders	Common	Headache	10 (7.2)

System Organ Class	Frequency	<Nexviazyme> patients (N = 138)	
		Preferred Term	Number of patients n (%)
	Common Common	Dizziness Tremor	4 (2.9) 2 (1.4)
Eye Disorders	Common	Ocular hyperaemia	2 (1.4)
Vascular Disorders	Common	Hypertension	2 (1.4)
Respiratory, thoracic, and mediastinal disorders	Common Common	Cough Dyspnea	3 (2.2) 3 (2.2)
Gastrointestinal disorders	Common Common Common Common Common	Nausea Diarrhea Vomiting Lip Swelling Swollen tongue	8 (5.8) 3 (2.2) 2 (1.4) 2 (1.4) 2 (1.4)
Skin and subcutaneous tissue disorders	Common Common Common Common Common	Pruritus Rash Urticaria Erythema Palmar erythema	13 (9.4) 11 (8.0) 9 (6.5) 4 (2.9) 2 (1.4)
Musculoskeletal and connective tissue disorders	Common Common Common	Muscle spasms Myalgia Pain in extremity	4 (2.9) 4 (2.9) 2 (1.4)
General disorders and administration site conditions	Common Common Common Common Common Common Common	Fatigue Chills Chest discomfort Pain Influzena-like illness Infusion site pain Asthenia	9 (6.5) 7 (5.1) 3 (2.2) 3 (2.2) 2 (1.4) 2 (1.4) 2 (1.4)
Investigation	Common Common	Blood pressure increased Oxygen saturation decreased	2 (1.4) 2 (1.4)

In a comparative study, EFC14028/COMET, 100 LOPD patients aged 16 to 78 naïve to enzyme replacement therapy were treated either with 20 mg/kg of Nexviazyme (n=51) or 20 mg/kg of alglucosidase

alfa (n=49). Serious adverse reactions were reported in 2% of patients treated with Nexviazyme and 6.1% of those treated with alglucosidase alfa. A total of 4 patients receiving alglucosidase alfa in the study permanently discontinued treatment due to adverse reactions; none of the patients from the Nexviazyme group permanently discontinued the treatment. The most frequently reported ADRs (>5%) were headache, nausea, pruritus, urticaria, and fatigue. IARs were reported in 25.5% of the patients treated with Nexviazyme compared to 32.7% of patients treated with alglucosidase alfa. The most frequently reported treatment-emergent IARs (>2 patients) in the avalglucosidase alfa group were pruritus and urticaria, and in the alglucosidase alfa group were nausea, pruritus, and flushing. Severe IARs were reported in 2 patients treated with alglucosidase alfa; there were no reports of severe IARs in patients treated with Nexviazyme.

ADR reported in at least 2 patients (≥2%) treated with Nexviazyme in the EFC14028/COMET study are listed in Table 2. The adverse reactions reported in other clinical studies with LOPD patients were dizziness, cough, dyspnea, erythema, muscle spasms, myalgia, chills, chest discomfort, and pain.

Table 2 - Adverse reactions reported in at least 2 patients (≥ 2%) treated with Nexviazyme in the COMET study

System Organ Class	Preferred Term	Nexviazyme (N=51) No. of patients n (%)	Alglucosidase alfa (N=49) No. of patients n (%)
Nervous system disorders	Headache	3 (5.9)	6 (12.2)
Gastrointestinal disorders	Nausea	3 (5.9)	5 (10.2)
	Diarrhea	2 (3.9)	0 (0)
	Vomiting	2 (3.9)	0 (0)
Skin and subcutaneous tissue disorders	Pruritus	4 (7.8)	4 (8.2)
	Urticaria	3 (5.9)	1 (2.0)
	Rash	2 (3.9)	3 (6.1)
General disorders and administration site conditions	Fatigue	3 (5.9)	3 (6.1)

In study 2, ACT14132/mini-COMET, adverse reactions in IOPD patients are based on exposure to 19 patients aged 1 to 12 years of age. Adverse reactions such as rash, urticaria, and pruritus occurred in 4 patients. There were no serious adverse reactions that occurred in the study. There were no deaths or discontinuation from the study because of adverse reactions.

POSTMARKETING

IMMUNOGENICITY

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Nexviazyme in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

The incidence of ADA response to avalglucosidase alfa in Nexviazyme-treated patients with Pompe disease is shown in Table 3. The median time to seroconversion was 8.3 weeks.

In treatment-naïve adult patients, the occurrence of IAR was observed in both ADA-positive and ADA- negative patients. Increase in the incidence of IAR and hypersensitivity were observed with higher IgG ADA titers. In enzyme replacement therapy (ERT) experienced adult patients, the occurrences of IARs and hypersensitivity were

higher in patients who developed treatment emergent ADA compared to patients who were ADA negative. One (1) treatment naïve patient and 1 treatment experienced patient developed anaphylaxis. The occurrences of IARs were similar between pediatric patients with ADA positive and negative status. There were no pediatric patients who developed anaphylactic reactions (refer warning/precaution section).

In clinical study EFC14028/COMET, 2 patients reported High Sustained Antibody Titers (HSAT) to Nexviazyme but this was not associated with a loss of efficacy. ADA cross reactivity studies showed that the majority of patients generate antibodies that are cross-reactive to alglucosidase alfa. At week 49, antibodies specific to Nexviazyme were detected in 3 (5.9%) patients. ADA did not impact measures of efficacy while limited impacts on PK and PD were observed primarily with high titer (refer pharmacology section).

Table 3 – Incidence of ADA response in patients with LOPD and IOPD

	Nexviazyme				**Alglucosidase alfa**	
	Treatment-naïve patients Avalglucosidase alfa ADA[a]	**Treatment-experienced patients[b] Avalglucosidase alfa ADA**			**In Primary analysis period - Alglucosidase alfa ADA**	
	Adults	**Adults**	**Pediatric**	**Pediatric**	**Adults**	**Pediatric**
	20 mg/kg every other week (N=61) N (%)	**20 mg/kg every other week**	**20 mg/kg every other week (N=6) N (%)**	**40 mg/kg every other week (N=10) N (%)**	**20 mg/kg every other week (N=48) N (%)**	**20 mg/kg every other week to 40 mg/kg every week mg/kg**
	(N=61) N (%)	**(N=55) N (%)**	**(N=6) N (%)**	**(N=10) N (%)**	**(N=48) N (%)**	**(N=6) N (%)**
ADA at baseline	2 (3.3)	40 (72.7)	1 (16.7)	1 (10)	2 (4.2)	3 (50)
Treatment emergent ADA	58 (95.1)	27 (49.1)	1(16.6)	5 (50)	46 (95.8)	3 (50)
Neutralizing antibody						
Both NAb types	13 (21.1)	2 (3.6)	0	0	ND[c]	ND[c]

Inhibition enzyme activity, only	4 (6.6)	8 (14.5)	0	0	4 (8.3)	2 (33.3)
Inhibition of enzyme uptake, only	10 (16.4)	8 (14.5)	0	0	19 (39.6)	0

[a]Includes one pediatric patient
[b]Treatment-experienced patients received alglucosidase alfa treatment before or during the clinical study within a range of 0.9- 9.9 years for adult patients and 0.5-11.7 years for pediatric patients.
[c]Not determined.

4.9 Overdose

IARs are more likely to occur with higher infusion rates (refer warning/precaution section).

In a clinical study, pediatric patients received doses up to 40 mg/kg of body weight every other week.

5 Pharmacological properties

5.1 Mechanism of Action

Pompe disease (also known as glycogen storage disease type II, acid maltase deficiency, and glycogenosis type II) is a rare metabolic muscle disease inherited in an autosomal recessive manner defined by a deficiency of acid α-glucosidase (GAA), which is necessary for the degradation of lysosomal glycogen.
GAA cleaves alpha-1,4 and alpha-1,6 linkages in glycogen under the acidic conditions of the lysosome. Pompe disease results in intra-lysosomal accumulation of glycogen in various tissues, particularly cardiac and skeletal muscles, leading to the development of cardiomyopathy, progressive muscle weakness, and impairment of respiratory function.

Avalglucosidase alfa is a recombinant human acid α-glucosidase (rhGAA) that provides an exogenous source of GAA. Avalglucosidase alfa is a modification of alglucosidase alfa in which approximately 7 hexamannose structures each containing 2 terminal mannose-6-phosphate (bis-M6P) moieties are conjugated to oxidized sialic acid residues on alglucosidase alfa. Avalglucosidase alfa has a 15-fold increase in mannose-6-phosphate (M6P) moieties compared with alglucosidase alfa. Increasing the level of bis-M6P on rhGAA provides a mechanism to drive uptake into the diaphragm and other skeletal muscle via the cation-independent M6P receptor, where it can degrade glycogen and ameliorate tissue damage.Binding to M6P receptors on the cell surface has been shown to occur via carbohydrate groups on the GAA molecule, after which it is internalized and transported into lysosomes, where it undergoes proteolytic cleavage that results in increased enzymatic activity.

5.2 Pharmacodynamic properties

In treatment naïve LOPD patients aged 16 to 78, the mean percentage (SD) change in urinary hexose tetrasaccharides from baseline for patients treated with 20 mg/kg every other week and alglucosidase alfa 20 mg/kg every other week was -53.90% (24.03) and -10.8% (32.33), respectively, week 49.

In pediatric IOPD patients (<18 years of age) treated with Nexviazyme at 40 mg/kg every other week who demonstrated either clinical decline (cohort 2) or sub-optimal clinical response (cohort 3) while on treatment with alglucosidase alfa, the mean percentage (SD) change in urinary hexose tetrasaccharides from baseline was -40.97% (16.72) and -37.48% (17.16), respectively, after 6 months. In patients previously declining treated with Nexviazyme at 20 mg/kg every other week, mean (SD) percentage change was 0.34% (42.09).

5.3 Pharmacokinetics properties

Patients with late-onset Pompe disease (LOPD)

The pharmacokinetics of avalglucosidase alfa was evaluated in a population analysis of 75 LOPD patients aged 16 to 78 years who received 5 to 20 mg/kg of avalglucosidase alfa every other week for up to 5 years.

Patients with infantile-onset Pompe disease (IOPD)

The pharmacokinetics of avalglucosidase alfa was characterized in 16 patients aged 1 to 12 years who were treated with avalglucosidase alfa, which included 6 patients treated with 20 mg/kg and 10 patients treated with 40 mg/kg doses every other week for up to 25 weeks.

Absorption

The exposure to avalglucosidase alfa increased in a dose-proportional manner between 5 to 20 mg/kg in LOPD patients and between 20 and 40 mg/kg in IOPD patients. No accumulation was observed following every other week dosing.

In LOPD patients, for a 4-hour IV infusion of 20 mg/kg every other week, the mean C_{max} and mean AUC_{2W} were 273 µg/mL (24%) and 1220 µg.h/mL (29%), respectively.

In IOPD patients, for a 4-hour IV infusion of 20 mg/kg every other week and 7-hour IV infusion for 40 mg/kg every other week, the mean C_{max} ranged from 175 to 189 µg/mL for the 20 mg/kg dose and 205 to 403 µg/mL for 40 mg/kg dose. The mean AUC_{2W} ranged from 805 to 923 µg•hr/mL for the 20 mg/kg dose and 1720 to 2630 µg•hr/mL for 40 mg/kg dose.

Distribution

In LOPD patients, the typical population PK model predicted central compartment volume of distribution of avalglucosidase alfa was 3.4 L.

In IOPD patients treated with avalglucosidase alfa 20 mg/kg and 40 mg/kg every other week, the mean volume of distribution at steady state ranged between 3.5 to 5.4 L.

Metabolism

The metabolic pathway of avalglucosidase alfa has not been characterized. As a glycoprotein, avalglucosidase alfa is expected to be degraded into small peptides or amino acids via non-saturable catabolic pathways.

Elimination

In LOPD patients, the typical population PK model predicted linear clearance was 0.87 L/h. Following 20 mg/kg every other week, the mean plasma elimination half-life was 1.55 hours.

In IOPD patients treated with avalglucosidase alfa 20 mg/kg and 40 mg/kg every other week, mean plasma clearance ranged from 0.53 to 0.70 L/h, and mean plasma elimination half-life from 0.60 to 1.19 hours.

Immunogenicity

In the study 1, EFC14028/COMET, 96.1% (49 of 51 patients) receiving Nexviazyme developed treatment-emergent ADA. As only 2 patients were ADA negative, therefore, the ADA impact on PK was assessed by categorizing the ADA-positive patients into 3 peak titer groups: ≤800, 1,600-6,400, and ≥12,800. Five patients had ≥50% change in the AUC at week 49 from baseline but no obvious pattern in titers. Inter- subject comparison of the AUC at Day 1 or 2 and week 49 supported the overall analysis of percent change in the AUC and ADA positivity categorized by ADA titers. In vitro evaluation of neutralizing antibodies that inhibited enzyme activity or inhibited cellular uptake demonstrated no clear relationship of assay positivity with AUC (refer adverse reaction section). The treatment experienced IOPD patients had titers ≤6,400, and as changes in PK were not observed, the relationship to ADA was not evaluated for this group.

Special populations

Population pharmacokinetic analyses in LOPD patients showed that body weight, age, and gender did not meaningfully influence the pharmacokinetics of avalglucosidase alfa.

Hepatic Impairment

The pharmacokinetics of avalglucosidase alfa has not been studied in patients with hepatic impairment.

Renal Impairment

No formal study of the effect of renal impairment on the pharmacokinetics of avalglucosidase alfa was conducted. On the basis of a population pharmacokinetic analysis of data from 75 LOPD patients receiving20 mg/kg, including 6 patients with mild renal impairment (glomerular filtration rate: 60 to 89 mL/min; at baseline), no relevant effect of renal impairment on exposure to avalglucosidase alfa was observed.

6 Nonclinical properties

6.1 Animal Toxicology or Pharmacology

SINGLE DOSE TOXICITY

No single-dose non-clinical toxicity studies were performed with Nexviazyme.

REPEAT DOSE TOXICITY

In a 26-week repeat-dose toxicity study, Nexviazyme was administered to monkeys via 6-hour IV infusion at a dose of 0, 50, or 200 mg/kg every other week. No adverse effects were observed. The NOAEL was 200 mg/kg every other week, the highest dose tested. The mean exposure following the 13th infusion at the NOAEL was 28 162 µg.hr/mL ($AUC_{0\text{-}inf}$).

GENOTOXICITY

Genotoxicity studies with Nexviazyme were not conducted.

CARCINOGENICITY

Carcinogenicity studies with Nexviazyme were not conducted.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

All reproductive toxicity studies in mice included pretreatment with DPH to prevent or minimize hypersensitivity reactions. The effects of Nexviazyme were evaluated based on comparison to a control group treated with DPH alone. Rabbits tested in reproductive toxicity studies were not pretreated with DPH because hypersensitivity reactions were not observed.

Fertility

In a combined sex fertility study in mice, the effects of Nexviazyme (0, 10, 20, or 50 mg/kg every other day IV) on mating performance, fertility, and early embryonic development were evaluated following the administration before to cohabitation (male mice: 10 weeks, female mice: 2 weeks), through conception, to Gestational Day (GD) 7. There were 4, 7, and 3 male mice and 2, 3, and 1 female mouse that were found dead in the 10, 20, and 50 mg/kg/dose groups, respectively. The cause of death was considered related to an immunologic response (including an anaphylactoid response). In male mice, there were no effects on mating index, fertility index, organ weights, macroscopic observations, or microscopic findings, and no changes in sperm parameters (sperm motility and density). In female mice, there were no effects on mating index, fertility index, organ weights, ovarian and uterine parameters, or microscopic evaluations. The male and female fertility NOAEL was 50 mg/kg/dose.

Embryo-Fetal Development

Pregnant mice were administered Nexviazyme at a dose of 0, 10, 20 or 50 mg/kg/day IV once daily on GD 6 through 15. Cesarean sections were performed on GD18. Placental transfer studies determined that avalglucosidase alfa is not transported from the maternal to the fetal circulation. There were 2 mice in the 50 mg/kg/day group found dead on GD14 that were considered related to an immunologic response (including an anaphylactoid response). Two deaths at 10 mg/kg/day were related to the blood collection procedure. There were no test article-related effects on

maternal body weight, macroscopic observations, pregnancy rate, mean number of corpora lutea, number of implants, live male or live female fetuses, number of live fetuses, number of dead fetuses, total number of fetuses, fetal body weight, fetal ossification site counts, or fetal external, visceral, or skeletal examinations. Increased post implantation loss and mean number of late resorptions were observed at 50 mg/kg/day group. The maternal NOAEL was 50 mg/kg/day IV (AUC_{0-24} = 2080 μg·h/mL), and the developmental NOAEL was 20 mg/kg/day IV (AUC_{0-24} = 582 μg·h/mL).

Pregnant rabbits were administered Nexviazyme at a dose of 0, 30, 60, and 100 mg/kg/day by IV infusion once daily from GD6–19. A statistically significant mean body weight loss was observed from GD19–20 at 100 mg/kg/day and lower mean body weight gain and food consumption were observed in the 60 and 100 mg/kg/day groups during the GD13–20 interval; mean food consumption in these groups was also lower when the entire treatment period (GD6–20) was evaluated. Intrauterine growth and survival were unaffected by maternal test article administration, and no test article-related malformations or developmental variations were observed. The maternal NOAEL was 30 mg/kg/day IV (GD19 AUC_{0-24} = 1260 μg*h/mL) and the embryo-fetal NOAEL was 100 mg/kg/day IV (maternal AUC_{0-24} on GD19 = 7910 μg.h/mL).

Pre- and Postnatal Development

Pregnant mice were administered 0, 10, 20 or 50 mg/kg/dose IV Nexviazyme once every other day from GD6 through PPD 20. DPH was administered before the administration of Nexviazyme starting with the fifth dose. There were no test article-related deaths in the F0 and F1 mice. Mortality or early euthanasia that occurred in F0 females included 2 at 10 mg/kg/dose (GD18 and Lactation Day (LD) 12), 1 at 20 mg/kg/dose (LD20), and 1 at 50 mg/kg/dose (GD16). Mortality or early euthanasia that occurred in F1 mice included 1 male at 0/5 mg/kg/dose DPH (PPD 29), 1 female at 0/0 (PPD 23), and 1 female at 20 mg/kg/dose (PPD71). There was no effect on F1 sexual maturation, neurobehavioral parameters (motor activity, acoustic startle habituation, or performance in a passive avoidance paradigm), mating and fertility parameters, macroscopic observations, testes and epididymides weights, cesarean section and litter parameters, or external embryonic examinations. The maternal NOAEL and the NOAEL for reproduction in the dams anfor viability and growth in the offspring were 50 mg/kg/dose IV.

OTHER TOXICITY STUDIES

Local Tolerance

Examination of the IV infusion sites in monkeys showed no adverse effects related to administration of Nexviazyme.

Juvenile Toxicity

In juvenile mice, the potential toxicity of Nexviazyme (0, 20, 50, or 100 mg/kg every other week IV in female mice and 0, 25, 50, or 100 mg/kg every other week IV in males) was evaluated following administration for approximately 9 weeks from Postnatal Day (PND) 21 through PND77 or PND91 (for male mice in the fertility cohort only). DPH (5 mg/kg) was administered to mice in treated groups due to the potential for hypersensitivity. There were 25 unscheduled deaths, including 15 male mice (1, 10, 3, and 1 at 0, 25, 50,and 100 mg/kg every other week, respectively) and 10 female mice (1, 7, and 2 at 0, 20, and 50 mg/kg every other week, respectively). Four of these deaths (1 male and 1 female mice at 0 mg/kg every other week, 1 male at 25 mg/kg every other week, and 1 female at 50 mg/kg every other week) were unrelated to Nexviazyme administration. The cause of death in the remaining mice was undetermined but was likely related to an immunologic response (including an anaphylactoid response). Increased total leukocyte counts, lymphocytes, monocytes, segmented neutrophils, basophils (20, 50, and 100 mg/kg every other week), and eosinophils (50 and 100 mg/kg every other week) were observed in surviving males, consistent with an immunologic (anaphylactoid) response. There were no avalglucosidase alfa-related effects on clinical observations, body weight, femur length, food consumption, clinical chemistry, bone density, organ weights, macroscopic observations, or microscopic findings. There were no effects on developmental neurobehavioral functional tests performed (open field, passive avoidance, auditory startle habituation, or motor activity), or on sexual maturation, estrous cyclicity, mating and fertility indices, or maternal body weight or food consumption. In addition, there were no effects on ovarian and uterine parameters, on the weights of male.

7 Description

Proprietary Name: NEXVIAZYME®
Generic or Official name: Avalglucosidase alfa
Chemical Name: Recombinant human acid α-glucosidase conjugated with synthetic bis-mannose-6- phosphate (bis-M6P).

8 Pharmaceutical properties

8.1. Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

8.2 Shelf- Life

SHELF-LIFE (UNOPENED VIALS – BEFORE RECONSTITUTION)

48 months when stored at 2°C to 8°C (36° to 46°F).

SHELF-LIFE (AFTER RECONSTITUTION AND DILUTION)

The reconstituted and diluted solution should be administered without delay. The reconstituted product can be stored up to 24 hours when refrigerated at 2°C and 8°C (36° to 46°F) and the diluted product can be stored up to 24 hours when refrigerated at 2°C to 8°C (36° to 46°F) and up to 9 hours (including infusion time) when stored at room temperature (up to 25C or 77°F).

8.3 Packaging Information

Nexviazyme is a sterile white to pale yellow lyophilized powder.

It is supplied in a 20 mL type I, colorless, clear, glass vial closed with 20 mm siliconized elastomeric stopper. The stoppered vials are crimped with an aluminum seal with a Flip-Off® button.

8.4 Storage and handling instructions

Store in a refrigerator between 2°C to 8°C (36° to 46°F). Do not use Nexviazyme after the expiration date on the vial.

SPECIAL HANDLING CONDITIONS

Vials are single use only. Any unused product should be discarded.

RECONSTITUTION, DILUTION, AND PREPARATION

Use aseptic technique during preparation.
1. Determine the number of vials to be reconstituted based on individual patient's weight and the recommended dose of 20 mg/kg or 40 mg/kg.
Patient weight (kg) x dose (mg/kg) = patient dose (in mg). Patient dose (in mg) divided by 100 mg/vial = number of vials to reconstitute. If the number of vials includes a fraction, round up to the next whole number.
Example: Patient weight (16 kg) x dose (20 mg/kg) = patient dose (320 mg). 320 mg divided by 100 mg/vial = 3.2 vials; therefore, 4 vials should be reconstituted.
Example: Patient weight (16 kg) x dose (40 mg/kg) = patient dose (640 mg).

640 mg divided by 100 mg/vial = 6.4 vials; therefore, 7 vials should be reconstituted.

2. Remove the required number of vials needed for the infusion from the refrigerator and set aside for approximately 30 minutes to allow them to reach room temperature.
3. Reconstitute each vial by slowly injecting 10.0 mL of Sterile water for injections (WFI) to each vial. Each vial will yield 100 mg/10 mL (10 mg/mL). Avoid forceful impact of the water for injection on the powder and avoid foaming. This is performed by slow drop-wise addition of the WFI down the inside of the vial and not directly onto the lyophilized cake. Tilt and roll each vial gently. Do not invert, swirl, or shake. Avoid any air introduction into the infusion bag during the dilution of the product.
4. Perform an immediate visual inspection on the reconstituted vials for particulate matter and discoloration. If upon immediate inspection particles are observed or if the solution is discolored, do not use. Allow the solution to become dissolved.
5. The reconstituted solution should be diluted in 5% dextrose in water to a final concentration of 0.5 mg/mL to 4 mg/mL. See Table 4 for the recommended total infusion volume based on the patient weight.
6. Slowly withdraw the volume of reconstituted solution from each vial (calculated according to patient's weight).
7. Add the reconstituted solution slowly and directly into the 5% dextrose solution. Avoid foaming or agitation of the infusion bag. Avoid air introduction into the infusion bag.
8. Gently invert or massage the infusion bag to mix. Do not shake.
9. It is recommended to use an in-line, low protein binding, 0.2 µm filter to administer Nexviazyme. After the infusion is complete, flush with 5% dextrose in water bag.
10. Do not infuse Nexviazyme in the same intravenous line with other products.

Table 4 - Projected intravenous infusion volumes for Nexviazyme administration by patient weight at 20 and 40 mg/kg Dose

Patient Weight Range (kg)	Total infusion volume for 20 mg/kg (mL)	Total infusion volume for 40 mg/kg (mL)
1.25 to 5	50	50
5.1 to 10	50	100
10.1 to 20	100	200
20.1 to 30	150	300
30.1 to 35	200	400
35.1 to 50	250	500
50.1 to 60	300	600
60.1 to 100	500	1000
100.1 to 120	600	1200
120.1 to 140	700	1400
140.1 to 160	800	1600
160.1 to 180	900	1800
180.1 to 200	1000	2000

9 Patient Counselling Information

HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS

Hypersensitivity reactions, including anaphylaxis, have been reported in Nexviazyme-treated patients. In clinical studies 60 (43.5%) patients experienced hypersensitivity reactions including 6 patients who reported severe hypersensitivity reactions and 2 patients who experienced anaphylaxis. Some of the hypersensitivity reactions were IgE mediated. Anaphylaxis symptoms included respiratory distress, chest pressure, generalized flushing, cough, dizziness, nausea, redness on palms, swollen lower lip, decreased breath sounds, redness on feet, swollen tongue, itchy palms and feet, and oxygen desaturation. Symptoms of severe hypersensitivity reactions included respiratory failure, respiratory distress and rash (refer warning/precautions section)

RISK OF ACUTE CARDIORESPIRATORY FAILURE

Caution should be exercised when administering Nexviazyme to patients susceptible to fluid volume overload or patients with acute underlying respiratory illness or compromised cardiac and/or respiratory function for whom fluid restriction is indicated. These patients may be at risk of serious exacerbation of their cardiac or respiratory status during infusion. Appropriate medical support and monitoring measures should be readily available during Nexviazyme infusion, and some patients may require prolonged observation times that should be based on the individual needs of the patient. (refer warning/precautions section)

10.Details of Manufacturer

Genzyme Ireland Limited, IDA Industrial Park, Old Kilmeaden Road, Waterford, Ireland, X91 TP27
(Manufacturing site, Formulation site, Primary Packaging Site, Secondary Packaging Site, Batch Release Site, Testing Site).

Importer:
Sanofi Healthcare India Private Limited, Gala No.4, Ground Floor, Building No Bl, City Link Warehousing Complex, S No. 121/ 10/A, 121/10/B And 69, NH3 Vadape Tal- Bhiwandi 16, Thane Z5, Bhiwandi, Maharashtra (India) – 421302.

11. Details of permission or license number with date: IMP/BIO/23/000066 dated 14-Jun-2023

12.Date of revision: Dec 2025

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