

NEXVIAZYME POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION 100 MG

1. NAME OF THE MEDICINAL PRODUCT

Nexviazyme Powder For Concentrate For Solution For Infusion 100 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg of avalglucosidase alfa.

After reconstitution, each vial contains a total extractable volume of 10.0 ml at a concentration of 10 mg of avalglucosidase alfa* per ml.

*Avalglucosidase alfa is a human acid α -glucosidase produced in Chinese hamster ovary cells (CHO) by recombinant DNA technology, which is subsequently conjugated with approximately 7 hexamannose structures (each containing two terminal mannose-6-phosphate (M6P) moieties) to oxidised sialic acid residues on the molecule, thereby increasing bis-M6P levels.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion

White to pale yellow lyophilised powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Nexviazyme treatment should be supervised by a physician experienced in the management of patients with Pompe disease or other inherited metabolic or neuromuscular diseases.

Posology

Patients may be pre-treated with antihistamines, antipyretics, and/or corticosteroids to prevent or reduce allergic reactions.

The recommended dose of avalglucosidase alfa is 20 mg/kg of body weight administered once every 2 weeks.

Dose modification for IOPD patients

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 increase 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).

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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. (see section 4.4).

Special populations

Elderly patients

No dose adjustment is required in patients >65 years.

Hepatic impairment

The safety and efficacy of avalglucosidase alfa in patients with hepatic impairment have not been evaluated and no specific dose regimen can be recommended for these patients.

Renal impairment

No dose adjustment is required in patients with mild renal impairment. The safety and efficacy of avalglucosidase alfa in patients with moderate or severe renal impairment have not been evaluated and no specific dose regimen can be recommended for these patients. (see section 5.2).

Paediatric population (patients 6 months of age and younger)

The safety and efficacy of avalglucosidase alfa in children 6 months of age and younger have not yet been established. There are no data available in patients 6 months of age and younger.

Method of administration

Nexviazyme vials are for single use only and the medicinal product should be administered as an intravenous infusion.

The infusion should be administered incrementally as determined by patient response and comfort. It is recommended that the infusion begins at an initial rate of 1 mg/kg/hour and is gradually increased every 30 minutes if there are no signs of infusion-associated reactions (IARs), in accordance with Table 1. Vital signs should be obtained at each step, before increasing the infusion rate.

Table 1 – Infusion rate schedule

Patient		Infusion rate (mg/kg/hour)					Approximate duration (h)
		step 1	step 2	step 3	step 4	step 5	
LOPD		1	3	5 ^a	7 ^a	NA	4 to 5
IOPD	4-step process	1	3	5	7	NA	7
	5-step process ^b	1	3	6	8	10 ^b	5

^a For LOPD patients with body weight of 1.25-5 kg a maximum infusion rate of 4.8 mg/kg/hour can be applied.

^b For IOPD patients with body weight of 1.25-5 kg a maximum infusion rate of 9.6 mg/kg/hour can be applied.

In the event of anaphylaxis or severe hypersensitivity reaction or severe IARs, administration of Nexviazyme should be immediately discontinued and appropriate medical treatment should be initiated. In the event of mild to moderate hypersensitivity reactions or IARs, the infusion rate may be slowed or temporarily stopped and/or appropriate medical treatment initiated (see section 4.4).

Symptoms may persist despite temporarily stopping the infusion; therefore, the treating physician should wait at least 30 minutes for symptoms of the reactions to resolve before deciding to stop the infusion for the remainder of the day. If symptoms subside, infusion rate should be resumed for 30 minutes at half the rate, or less, of the rate at which the reactions occurred, followed by an increase in infusion rate by 50% for 15 to 30 minutes. If symptoms do not recur, the infusion rate should be increased to the rate at which the reactions occurred and consider continuing to increase the rate in a stepwise manner until the maximum rate is achieved.

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Home infusion

Infusion of Nexviazyme at home may be considered for patients who are tolerating their infusions well and have no history of moderate or severe IARs for a few months. The decision to have a patient move to home infusion should be made after evaluation and upon recommendation by the treating physician. A patient's underlying co-morbidities and ability to adhere to the home infusion requirements need to be taken into account when evaluating the patient for eligibility to receive home infusion. The following criteria should be considered:

- The patient must have no ongoing concurrent condition that, in the opinion of the physician, may affect patient's ability to tolerate the infusion.
- The patient is considered medically stable. A comprehensive evaluation must be completed before the initiation of home infusion.
- The patient must have received Nexviazyme infusions supervised by a physician with expertise in management of Pompe patients for a few months that could be in a hospital or in another appropriate setting of outpatient care. Documentation of a pattern of well-tolerated infusions with no IARs, or mild IARs that have been controlled with premedication, is a prerequisite for the initiation of home infusion.
- The patient must be willing and able to comply with home infusion procedures.
- Home infusion infrastructure, resources, and procedures, including training, must be established and available to the healthcare professional. The healthcare professional should be available at all times during the home infusion and a specified time after infusion, depending on patient's tolerance prior to starting home infusion.

If the patient experiences adverse reactions during the home infusion, the infusion process should be stopped immediately, and appropriate medical treatment should be initiated (see section 4.4). Subsequent infusions may need to occur in a hospital or in an appropriate setting of outpatient care until no such adverse reaction is present. Dose and infusion rate must not be changed without consulting the responsible physician.

For instructions on reconstitution and dilution of medicinal product before administration, see section 6.6.

4.3 Contraindications

Life-threatening hypersensitivity to the active substance or to any of the excipients listed in section 6.1 when re-challenge was unsuccessful. (see sections 4.4 and 4.8)

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity reactions (including anaphylaxis)

Hypersensitivity reactions, including anaphylaxis, have been reported in Nexviazyme-treated patients (see section 4.8).

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.

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In patients with severe hypersensitivity, desensitization procedure to Nexviazyme may be considered. If the decision is made to re-administer the medicinal 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 (IARs)

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 (see section 4.8).

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 pre-treatment.

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 mild or moderate IARs occur regardless of pre-treatment, decreasing the infusion rate or temporarily stopping the infusion may ameliorate the symptoms (see section 4.8).

Immunogenicity

Treatment emergent anti-drug antibodies (ADA) were reported in both treatment naïve (95%) and treatment-experienced patients (49%) (see section 4.8).

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 clinical studies, the development of ADA did not impact clinical efficacy (see section 4.8).

Immunoglobulin G (IgG) antibody titres should be regularly monitored and IgG ADA testing should 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 anaesthesia for central venous catheter placement

Caution should be used when administering general anaesthesia for the placement of a central venous catheter or for other surgical procedures in patients with IOPD with cardiac hypertrophy.

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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 anaesthesia in IOPD patients with cardiac hypertrophy.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Because it is a recombinant human protein, avalglucosidase alfa is an unlikely candidate for cytochrome P450 mediated drug-drug interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no available data on the use of Nexviazyme in pregnant women. Animal studies do not indicate direct harmful effects with respect to reproductive toxicity. Indirect foetal effects in mice were considered related to an anaphylactic response to avalglucosidase alfa (see section 5.3). The potential risk for humans is unknown. 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 foetus.

Breast-feeding

There are no available data on the presence of Nexviazyme in human milk or the effects of Nexviazyme on milk production or the breast-fed infant. No conclusions can be drawn regarding whether or not Nexviazyme is safe for use during breast-feeding. Nexviazyme should be used during breast-feeding only if the potential benefits to the mother outweigh the potential risks, including those to the breast-fed child (see section 5.3).

Fertility

There are no clinical data on the effects of Nexviazyme on human fertility. Animal studies in mice showed no impairment of male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Nexviazyme may have a minor influence on the ability to drive and use machines. Because dizziness, hypotension and somnolence have been reported as IARs, this may affect the ability to drive and use machines on the day of the infusion (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Serious adverse reactions reported in patients treated with Nexviazyme were chills in 1.4% of patients and in 0.7% of patients each were headache, dyspnoea, respiratory distress, nausea, skin discoloration, chest discomfort, pyrexia, blood pressure increased, body temperature increased, heart rate increased, and oxygen saturation decreased. Hypersensitivity reactions were reported in 43.5% of patients, anaphylaxis in 1.4%, and IARs in 26.1% in patients. A total of 2.9% patients receiving Nexviazyme in clinical studies permanently discontinued treatment; 0.7% patients each discontinued the treatment because of the following events considered to be related to Nexviazyme: respiratory distress, chest discomfort, dizziness, cough, nausea, flushing, ocular hyperaemia, and erythema.

The most frequently reported adverse drug reactions (ADRs) (>5%) were pruritus (9.4%), rash (8%), headache (7.2%), urticaria (6.5%), fatigue (6.5%), nausea (5.8%), and chills (5.1%).

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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 paediatric patients) treated with Nexviazyme. ADRs reported in patients treated with Nexviazyme in the pooled analysis of clinical studies are listed in Table 2.

Tabulated list of adverse reactions

Adverse reactions (reported in at least 3 patients) per System Organ Class, presented by frequency categories: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the available data).

Due to the small patient population, an adverse reaction reported in 2 patients is classified as common. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2 – Adverse reactions occurring in patients treated with Nexviazyme in a pooled analysis of clinical studies (N=138)

System organ class	Frequency	Preferred term
Infections and infestations	Uncommon	Conjunctivitis
Immune Disorders	Very common Common	Hypersensitivity Anaphylaxis
Nervous system disorders	Common Common Common Uncommon Uncommon	Headache Dizziness Tremor Paraesthesia Somnolence
Eye Disorders	Common Uncommon Uncommon Uncommon	Ocular hyperaemia Conjunctival hyperaemia Eye pruritus Lacrimation increased
Cardiac Disorders	Uncommon Uncommon	Tachycardia Ventricular extrasystoles
Vascular Disorders	Common Uncommon Uncommon	Hypertension Flushing Hypotension
Respiratory, thoracic, and mediastinal disorders	Common Common Uncommon Uncommon Uncommon Uncommon	Cough Dyspnoea Tachypnoea Laryngeal oedema Respiratory distress Throat irritation
Gastrointestinal disorders	Common Common Common Common Common Uncommon Uncommon Uncommon Uncommon Uncommon	Nausea Diarrhoea Vomiting Lip swelling Swollen tongue Abdominal pain Hypoaesthesia oral Paraesthesia oral Dysphagia Dyspepsia
Skin and subcutaneous tissue disorders	Common Common Common Common Common Uncommon Uncommon Uncommon	Pruritus Rash Urticaria Erythema Palmer erythema Angioedema Hyperhidrosis Skin discolouration
Musculoskeletal and connective tissue disorders	Common Common Uncommon	Muscle spasms Myalgia Pain in extremity
General disorders and administration site conditions	Common Common Common Common Common Common Uncommon Uncommon Uncommon Uncommon Uncommon Uncommon	Fatigue Chills Chest discomfort Pain Influenza-like illness Infusion site pain Facial pain Hyperthermia Infusion site extravasation Infusion site joint pain Infusion site rash Infusion site reaction

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System organ class	Frequency	Preferred term
	Uncommon	Infusion site urticaria
	Uncommon	Localized oedema
	Uncommon	Peripheral swelling
	Uncommon	Pyrexia
	Uncommon	Asthenia
Investigation	Common	Blood pressure increased
	Common	Oxygen saturation decreased
	Uncommon	Body temperature increase
	Uncommon	Heart rate increased
	Uncommon	Breath sounds abnormal
	Uncommon	Complement factor increased
	Uncommon	Immune complex level increased

Table 2 includes treatment related adverse events that are considered biologically plausibly related to avalglucosidase alfa based on the alglucosidase alfa Package Insert.

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 8.2% 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.

Description of selected adverse reactions

Hypersensitivity (including anaphylaxis)

In a pooled safety analysis, 60/138 (43.5%) patients experienced hypersensitivity reactions including 6/138 (4.3%) patients who reported severe hypersensitivity reactions and 2/138 (1.4%) patients who experienced anaphylaxis. Some of the hypersensitivity reactions were IgE mediated. Anaphylaxis symptoms included respiratory distress, chest pressure, generalised 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.

Infusion-associated reactions (IARs)

In a pooled safety analysis, IARs were reported in approximately 42/138 (30.4%) of patients treated with avalglucosidase alfa in clinical studies. Severe IARs were reported in 3/138 (2.2%) of patients including symptoms of chest discomfort, nausea, and increased blood pressure. IARs reported in more than 1 patient included chills, cough, diarrhoea, erythema, fatigue, headache, influenza-like illness, nausea, ocular hyperaemia, 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.

In the comparative study EFC14028/COMET study, fewer LOPD patients in the avalglucosidase alfa group reported at least 1 IAR (13/51 [25.5%]) in comparison to the alglucosidase alfa group (16/49 [32.7%]). Severe IARs were not reported in patients in the avalglucosidase alfa group and reported in 2 patients in the alglucosidase alfa group (dizziness, visual impairment, hypotension, dyspnoea, cold sweat, and chills). The most frequently reported TEAEs (>2 patients) in the avalglucosidase alfa group were pruritus (7.8%) and urticaria (5.9%) and in the alglucosidase alfa group were nausea (8.2%), pruritus (8.2%), and flushing (6.1%). The majority of IARs reported in 7 (13.7%) patients were of mild severity in the avalglucosidase alfa group and 10 [20.4%] patients in the alglucosidase alfa group).

Immunogenicity

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.

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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 titres. In treatment-naïve patients, a trend for increases in the incidence of IARs was observed with increasing ADA titres, with the highest incidence of IARs (61.5%) reported in the high ADA peak titre range $\geq 12,800$, compared with an incidence of 17.2% in patients with intermediate ADA titre 1,600-6,400, an incidence of 7.1% in those with low ADA titre 100-800 and an incidence of 33.3% in those who were ADA negative. 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 paediatric patients with ADA positive and negative status. There were no paediatric patients who developed anaphylactic reactions (see section 4.4).

In clinical study EFC14028/COMET, 2 patients reported High Sustained Antibody Titres (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 α -glucosidase. 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 titre patients (see section 5.2).

Table 3 – Treatment emergent ADA incidence in LOPD and IOPD patient population

	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 20 mg/kg every other week	Adults 20 mg/kg every other week	Paediatric 20 mg/kg every other week	Paediatric 40 mg/kg every other week	Adults 20 mg/kg every other week	Paediatric 20 mg/kg every other week to 40 mg/kg every week
	(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 (16.7)	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 paediatric 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 paediatric patients.

^c Not determined

Paediatric population

Adverse drug reactions reported from clinical studies in the paediatric population (19 paediatric patients with IOPD between 1-12 years of age (mean age of 6.8) and one 16-year-old paediatric patient with LOPD) were similar to those reported in adults.

4.9 Overdose

Excessive infusion rate of Nexviazyme may result in hot flush. In a clinical study, paediatric patients received doses up to 40 mg/kg of body weight once every 2 weeks and no specific signs and symptoms were identified following the higher doses. For management of adverse reactions, see sections 4.4 and 4.8.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products, enzymes, ATC code:

A16AB22

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Mechanism of action

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. Binding to M6P receptors on the cell surface has been shown to occur via carbohydrate groups on the GAA molecule, after which it is internalised and transported into lysosomes, where it undergoes proteolytic cleavage that results in increased enzymatic activity to degrade glycogen.

Clinical efficacy and safety

Clinical studies in patients with LOPD

Study 1, EFC14028/COMET, was a multinational, multicentre, randomised, double-blinded study comparing the efficacy and safety of Nexviazyme and alglucosidase alfa in 100 treatment-naïve LOPD patients aged 16 to 78 years of age at the initiation of treatment. Patients were randomised 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 once every other week for 12 months (49 weeks). The study included an open-label, long-term, follow-up phase of up to 5 years for all patients, in which patients in the alglucosidase alfa arm were switched to treatment with Nexviazyme.

The primary endpoint of study 1 was the change in FVC % predicted in the upright position from baseline to 12 months (week 49). At week 49, the LS mean change (SE) in FVC % predicted for patients treated with Nexviazyme and alglucosidase alfa was 2.89% (0.88) and 0.46% (0.93), respectively. The clinically significant LS mean difference of 2.43% (95% CI: -0.13, 4.99) between Nexviazyme and alglucosidase alfa in FVC % predicted exceeded the pre-defined non-inferiority margin of -1.1 and achieved statistical non-inferiority ($p=0.0074$). The study did not demonstrate statistical significance for superiority ($p=0.0626$) and the testing of the secondary endpoints was performed without multiplicity adjustment.

The results for the primary endpoint are detailed in Table 4.

Table 4 – LS Mean change from baseline to week 49 in FVC % predicted in upright position

		Nexviazyme (n=51)	Alglucosidase Alfa (n=49)
Forced Vital Capacity % predicted in upright position			
Pre-treatment baseline	Mean (SD)	62.55 (14.39)	61.56 (12.40)
Week 13	LS mean (SE) change from baseline	3.05 (0.78)	0.65 (0.81)
Week 25	LS mean (SE) change from baseline	3.21 (0.80)	0.57 (0.84)
Week 37	LS mean (SE) change from baseline	2.21 (1.00)	0.55 (1.05)
Week 49	Mean (SD)	65.49 (17.42)	61.16 (13.49)
Estimated change from baseline to week 49 (MMRM)	LS mean (SE) change from baseline	2.89 ^a (0.88)	0.46 ^a (0.93)
Estimated difference between groups in change from baseline to week 49 (MMRM)	LS mean (95% CI) p-value ^b p-value ^c	2.43 ^a (-0.13,4.99) 0.0074 0.0626	

MMRM: mixed model repeated measure.

^a On the basis of MMRM model, the model includes baseline FVC % predicted(as continuous), sex, age (in years at baseline), treatment group, visit, interaction term between treatment group and visit as fixed effects.

^b Non-inferiority margin of -1.1%

^c Superiority not achieved

The key secondary endpoint of study 1 was change in total distance walked in 6 minutes (6-Minute Walk Test, 6MWT) from baseline to 12 months (week 49). At week 49, the LS mean change from baseline (SE) in 6MWT for patients treated with Nexviazyme and alglucosidase alfa was 32.21 m (9.93) and 2.19 m (10.40) respectively. The LS mean difference of 30.01 m (95% CI: 1.33,58.69) showed numerical improvement with Nexviazyme compared with alglucosidase alfa. The results for the 6MWT are detailed in Table 5. Additional secondary endpoints of the study were maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), Hand-held dynamometry (HHD) summary score, quick motor function test (QMFT) total score, and SF-12 (health-related survey on quality of life, both physical and mental component scores). The results for these endpoints are detailed in Table 5.

In treatment-naïve LOPD patients aged 16 to 78, the mean percentage (SD) change in urinary hexose tetrasaccharides from baseline for patients treated with Nexviazyme 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, in week 49.

Table 5 – LS mean change from baseline to week 49 for additional secondary endpoints

Endpoint	Nexviazyme LS mean change (SE)	Alglucosidase Alfa LS mean change (SE)	LS mean difference (95% CI)
6-minute walk test (6MWT) distance (meters) ^{a,b}	32.21 (9.93)	2.19 (10.40)	30.01 (1.33, 58.69)
Maximum Inspiratory Pressure (MIP) (%) predicted) ^c	8.70 (2.09)	4.29 (2.19)	4.40 (-1.63, 10.44)
Maximum Expiratory Pressure (% predicted) ^c	10.89 (2.84)	8.38 (2.96)	2.51 (-5.70, 10.73)
Hand-held dynamometry (HHD) summary scores	260.69 (46.07)	153.72 (48.54)	106.97 (-26.56, 240.5)
Quick Motor function Test (QMFT) total score	3.98 (0.63)	1.89 (0.69)	2.08 (0.22, 3.95)
Health-related survey on quality of life (SF-12)	PCS ^d score: 2.37 (0.99) MCS ^e score: 2.88 (1.22)	1.60 (1.07) 0.76 (1.32)	0.77 (-2.13, 3.67) 2.12 (-1.46, 5.69)

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

^bLS mean (SE) change from baseline at Weeks 13, 25, and 37 was 18.02 (8.79), 27.26 (9.98), and 28.43 (9.06), respectively, in the avalglucosidase alfa group and 15.11 (9.16), 9.58 (10.41), and 15.49 (9.48), respectively, in the alglucosidase alfa group.

^cPost-hoc sensitivity analysis excluding 4 patients (2 in each treatment arm) with supraphysiologic baseline MIP and MEP values.

^dPhysical Component Summary.

^eMental Component Summary.

In the EFC14028/COMET study, efficacy data were available in 24 patients at week 97, 17 patients at week 121, and 11 patients at week 145. Additionally, 9 patients randomised to alglucosidase alfa who switched the treatment to avalglucosidase alfa after week 49 continued the treatment for up to 2 years. FVC % predicted values remained elevated over baseline throughout dosing with avalglucosidase alfa for as long as 97 weeks in 24 patients who had reached this timepoint. Efficacy data in EFC14028/COMET study at week 97 for patients who switched from alglucosidase alfa to avalglucosidase alfa at week 49 showed numerical improvement for FVC % predicted and 6MWT. In the same study, the observed mean 6MWT distance remained elevated over baseline throughout dosing with avalglucosidase alfa for as long as 145 weeks in 10 patients who had reached this timepoint.

In an open-label, uncontrolled study in LOPD patients, the FVC % predicted and 6MWT showed maintenance of effect during the long-term treatment with avalglucosidase alfa 20 mg/kg every other week for up to 6 years.

Clinical study in patients with IOPD

Study 2, ACT14132/mini-COMET, was a multi-stage, phase 2, open-label, multicentre, multinational, repeated ascending dose cohort of Nexviazyme in paediatric IOPD patients (1-12 years of age) who demonstrated either clinical decline or sub-optimal clinical response while on treatment with alglucosidase alfa. The study enrolled a total of 22 patients; cohort 1 had 6 patients who demonstrated clinical decline and received 20 mg/kg every other week for 25 weeks, cohort 2 had 5 patients who demonstrated clinical decline and received 40 mg/kg every other week for 25 weeks, and cohort 3 had 11 patients who demonstrated sub-optimal response and received either Nexviazyme at 40 mg/kg every other week for 25 weeks (5 patients) or alglucosidase alfa at their stable pre-study dose (ranging between 20 mg/kg every other week and 40 mg/kg weekly) for 25 weeks (6 patients).

The primary objective of study 2 was to evaluate the safety and tolerability of administering Nexviazyme. The secondary objective was to determine the efficacy of Nexviazyme. Data showed stabilization or improvement in efficacy outcomes of gross motor function classification measure-88 (GMFM-88), quick motor function test (QMFT), Pompe paediatric evaluation of disability inventory (Pompe-PEDI), left ventricular mass (LVM) Z score, eyelid position measurements in patients

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previously declining or insufficiently controlled with alglucosidase alfa. Treatment effect was more pronounced with 40 mg/kg every other week compared to the 20 mg/kg every other week. Two out of six patients treated with Nexviazyme at 20 mg/kg every other week (cohort 1) demonstrated further clinical decline and received dose increase from 20 to 40 mg/kg every other week at week 55 and 61 respectively. All patients who received 40 mg/kg every other week maintained this dose for the duration of the study without further clinical decline.

In paediatric 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).

The long-term effects of treatment with Nexviazyme were evaluated in 10 patients at week 49, 8 patients at week 73, and 3 patients at week 97. In patients with IOPD previously declining with alglucosidase alfa, the efficacy on specific parameters of decline, including motor function, cardiac left ventricular mass, and eyelid position measurements, was sustained up to 2 years.

Paediatric population

Nineteen paediatric patients aged from 1 to 12 years with IOPD previously treated with alglucosidase alfa have been treated with Nexviazyme (see section 4.2 and 4.8) and two paediatric patients aged 9 and 16 years with LOPD was treated with Nexviazyme.

Pompe registry

Medical or healthcare professionals are encouraged to register patients who are diagnosed with Pompe disease at www.registrynxt.com. Patient data will be anonymously collected in this registry. The objectives of the “Pompe registry” are to enhance the understanding of Pompe disease and to monitor patients and their response to enzyme replacement therapy over time, with the ultimate goal of improving clinical outcomes for these patients.

5.2 Pharmacokinetic 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.

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. All patients were treatment-experienced.

Absorption

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.

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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.

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.

Linearity/non-linearity

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.

Immunogenicity

In the study 1, EFC14028/COMET, 96.1% (49 of 51 patients) receiving Nexviazyme developed treatment-emergent ADA. No clear trend of ADA impact on PK was observed.

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 receiving 20 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 avalglucosidase alfa exposure was observed.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity that included safety pharmacology endpoints.

Avalglucosidase alfa caused no adverse effects in a combined male and female fertility study in mice up to 50 mg/kg IV every other day (9.4 times the human steady-state AUC at the recommended biweekly dose of 20 mg/kg for patients with LOPD) (see section 4.6).

In an embryo-foetal toxicity study in mice, administration of avalglucosidase at the highest dose of 50 mg/kg/day (17 times the human steady-state AUC at the recommended biweekly dose of 20 mg/kg for patients with LOPD) produced increased post-implantation loss and mean number of late resorptions. No effects were seen at 20 mg/kg/day (4.8 times the human steady-state AUC at the recommended

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biweekly dose of 20 mg/kg for patients with LOPD). Avalglucosidase alfa does not cross the placenta in mice, suggesting that the embryo-foetal effects at 50 mg/kg/day were related to maternal toxicity from the immunologic response. No malformations or developmental variations were observed.

No adverse effects were observed in an embryo-foetal toxicity study in rabbits administered avalglucosidase alfa up to 100 mg/kg/day IV (91 times the human steady-state AUC at the recommended biweekly dose of 20 mg/kg for patients with LOPD).

There were no adverse effects in a pre- and post-natal developmental toxicity study in mice following administration of avalglucosidase alfa once every other day. The NOAEL for reproduction in the dams and for viability and growth in the offspring was 50 mg/kg every other day IV.

In juvenile mice, avalglucosidase alfa was generally well tolerated following administration for 9 weeks at doses up to 100 mg/kg every other week IV (~2 to 5 times the human steady-state AUC at the recommended biweekly dose of 40 mg/kg for patients with IOPD). However, the highest dose tested in juvenile animals is not enough to discard a potential risk for IOPD patients at 40 mg/kg based on exposure margin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine hydrochloride monohydrate
Glycine
Mannitol
Polysorbate 80

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vials: 4 years

Reconstituted medicinal product

After reconstitution, chemical, physical, and microbiological in-use stability has been demonstrated for 24 hours at 2°C - 8°C.

From a microbiological point of view, the reconstituted product should be used immediately.

If not used for dilution immediately, in-use storage times and conditions prior to dilution are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

Diluted medicinal product

After dilution, chemical, physical and microbiological in-use stability has been demonstrated between 0.5 mg/ml and 4 mg/ml for 24 hours at 2°C - 8°C, followed by 9 hours at room temperature (up to 25°C) to allow for infusion.

Use Aseptic Techniques.

From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally

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not be longer than 24 hours at 2°C - 8°C, followed by 9 hours at room temperature (up to 25°C) to allow for infusion.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

100 mg of powder for concentrate for solution for infusion in a vial (type I glass) with a stopper (elastomeric rubber), seal (aluminium) and a flip off cap.

Each pack contains 1, 5, 10, or 25 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Vials are for single use only.

Reconstitution

Aseptic technique should be used during reconstitution.

1. The number of vials have to be determined to be reconstituted based on individual patient's weight and the recommended dose of 20 mg/kg or 40 mg/kg.
Patient weight (kg) × 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, it should be rounded up to the next whole number.
Example: Patient weight (16 kg) × 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) × 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. The required number of vials needed for the infusion should be removed from the refrigerator and set aside for approximately 30 minutes to allow them to reach room temperature.
3. Each vial should be reconstituted by slowly injecting 10.0 ml of water for injections (WFI) to each vial. Each vial will yield 100 mg/10 ml (10 mg/ml). Forceful impact of the WFI on the powder and foaming should be avoided. This is performed by slow drop-wise addition of the WFI down the inside of the vial and not directly onto the lyophilised powder. Each vial should be tilted and rolled gently to dissolve the lyophilised powder. It should not be inverted, swirled, or shaken.
4. Immediate visual inspection should be performed on the reconstituted vials for particulate matter and discoloration. If upon immediate inspection particles are observed or if the solution is discoloured, the reconstituted medicinal product should not be used. The solution should be allowed to become dissolved.

Dilution

5. The reconstituted solution should be diluted in 5% glucose in water to a final concentration of 0.5 mg/ml to 4 mg/ml. See Table 6 for the recommended total infusion volume based on the patient weight.
6. The volume of reconstituted solution from each vial should be slowly withdrawn (calculated according to patient's weight).
7. The reconstituted solution should be added slowly and directly into the 5% glucose solution. Foaming or agitation of the infusion bag should be avoided. Air introduction into the infusion bag should be avoided.

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8. To mix the infusion bag solution, gently invert or massage the infusion bag to mix. It should not be shaken.
9. To avoid administration of inadvertently introduced particles during dose IV preparation, it is recommended to use an in-line, low protein binding, 0.2 µm filter to administer Nexviazyme. After the infusion is complete, the intravenous line should be flushed with glucose 5% in water.
10. Nexviazyme should not be infused in the same intravenous line with other medicinal products.

Table 6 – 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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Manufactured by
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