ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Nexviadyme 100 mg powder for concentrate for solution for infusion

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

Nexviadyme (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

Nexviadyme 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 (infantile-onset Pompe disease) 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).

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

Nexviadyme 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

Recommended Dose		**Infusion rate (mg/kg/hour)**					**Approximate duration (h)**
		step 1	**step 2**	**step 3**	**step 4**	**step 5**	
20 mg/kg		1	3	5[a]	7[a]	NA	4 to 5
40 mg/kg	4-step process	1	3	5	7	NA	7
	5-step process[b]	1	3	6	8	10[b]	5

[a] For patients with a recommended dose of 20 mg/kg and body weight of 1.25-5 kg a maximum infusion rate of 4.8 mg/kg/hour can be applied.
[b] For IOPD patients who experience lack of improvement a dose increase to 40 mg/kg every other week is recommended. For a 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 Nexviadyme 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.

Home infusion
Infusion of Nexviadyme 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 Nexviadyme 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 Nexviadyme-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 Nexviadyme is administered.

If severe hypersensitivity or anaphylaxis occur, Nexviadyme should be discontinued immediately, and appropriate medical treatment should be initiated. The risks and benefits of re-administering Nexviadyme 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 Nexviadyme 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 Nexviadyme and were more likely with higher infusion rates (see section 4.8).

Patients with an acute underlying illness at the time of Nexviadyme 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 Nexviadyme should be considered and appropriate medical treatment should be initiated. The benefits and risks of re-administering Nexviadyme 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 (62%) (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).

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.

Contact your local Sanofi representative or Sanofi EU Medical Services for information on the Sanofi Speciality Care testing services.

Risk of acute cardiorespiratory failure

Caution should be exercised when administering Nexviadyme 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 Nexviadyme 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.

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 Nexviadyme 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 Nexviadyme is safe for use during pregnancy. Nexviadyme 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 Nexviadyme in human milk or the effects of Nexviadyme on milk production or the breast-fed infant. No conclusions can be drawn regarding whether or not Nexviadyme is safe for use during breast-feeding. Nexviadyme 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 Nexviadyme 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

Nexviadyme 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 Nexviadyme were respiratory distress and chills in 1.4% of patients and in 0.7% of patients each were headache, dyspnoea, hypoxia, tongue oedema, nausea, pruritis, urticaria, skin discoloration, chest discomfort, pyrexia, blood pressure increased or decreased, body temperature increased, heart rate increased, and oxygen saturation decreased. Hypersensitivity reactions were reported in 60.6% of patients, anaphylaxis in 2.8%, and IARs in 39.4% in patients. A total of 4.9% of patients receiving Nexviadyme in clinical studies permanently discontinued treatment; 2.8% of patients each discontinued the treatment because of the following events considered to be related to Nexviadyme: respiratory distress, chest discomfort, dizziness, cough, nausea, flushing, ocular hyperaemia, urticaria, and erythema.

The most frequently reported adverse drug reactions (ADRs) (>5%) were pruritus (13.4%), nausea (12%), headache (10.6%), rash (10.6%), urticaria (8.5%), chills (7.7%), fatigue (7.7%), and erythema (5.6%).

The pooled safety analysis from 4 clinical studies (EFC14028/COMET, ACT14132/mini-COMET, TDR12857/NEO, and LTS13769/NEO-EXT) included a total of 142 patients (118 adult and 24 paediatric patients (1 paediatric patient directly enrolled in the open-label extension period of Study 1)) treated with Nexviadyme. ADRs reported in patients treated with Nexviadyme in the pooled analysis of clinical studies are listed in Table 2.

Tabulated list of adverse reactions

Adverse reactions per System Organ Class, presented by frequency categories: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥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 Nexviadyme in a pooled analysis of clinical studies (N=142)

System organ class	Frequency	Preferred term
Infections and infestations	Uncommon	Conjunctivitis
Immune Disorders	Very common	Hypersensitivity
	Common	Anaphylaxis
Nervous system disorders	Very common	Headache
	Common	Dizziness
	Common	Tremor
	Common	Somnolence
	Common	Burning sensation
	Uncommon	Paraesthesia
Eye Disorders	Common	Ocular hyperaemia
	Common	Conjunctival hyperaemia
	Common	Eye pruritus
	Common	Eyelid oedema
	Uncommon	Lacrimation increased
Cardiac Disorders	Common	Tachycardia
	Uncommon	Ventricular extrasystoles
Vascular Disorders	Common	Hypertension
	Common	Flushing
	Common	Hypotension
	Common	Cyanosis
	Common	Hot flush
	Common	Pallor
Respiratory, thoracic, and mediastinal disorders	Common	Cough
	Common	Dyspnoea
	Common	Respiratory distress
	Common	Throat irritation
	Common	Oropharyngeal pain
	Uncommon	Tachypnoea
	Uncommon	Laryngeal oedema
Gastrointestinal disorders	Very common	Nausea
	Common	Diarrhoea
	Common	Vomiting
	Common	Lip swelling
	Common	Swollen tongue
	Common	Abdominal pain
	Common	Abdominal pain upper

System organ class	Frequency	Preferred term
	Common	Dyspepsia
	Uncommon	Hypoaesthesia oral
	Uncommon	Paraesthesia oral
	Uncommon	Dysphagia
Skin and subcutaneous tissue disorders	Very common	Pruritus
	Very common	Rash
	Common	Urticaria
	Common	Erythema
	Common	Palmer erythema
	Common	Hyperhidrosis
	Common	Rash erythematous
	Common	Rash pruritic
	Common	Skin plaque
	Uncommon	Angioedema
	Uncommon	Skin discolouration
Musculoskeletal and connective tissue disorders	Common	Muscle spasms
	Common	Myalgia
	Common	Pain in extremity
	Common	Flank pain
General disorders and administration site conditions	Common	Fatigue
	Common	Chills
	Common	Chest discomfort
	Common	Pain
	Common	Influenza-like illness
	Common	Infusion site pain
	Common	Pyrexia
	Common	Asthenia
	Common	Face oedema
	Common	Feeling cold
	Common	Feeling hot
	Common	Sluggishness
	Uncommon	Facial pain
	Uncommon	Hyperthermia
	Uncommon	Infusion site extravasation
	Uncommon	Infusion site joint pain
	Uncommon	Infusion site rash
	Uncommon	Infusion site reaction
	Uncommon	Infusion site urticaria
	Uncommon	Localized oedema
	Uncommon	Peripheral swelling
Investigation	Common	Blood pressure increased
	Common	Oxygen saturation decreased
	Common	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 SmPC.

In a comparative study, EFC14028/COMET, 100 LOPD (late-onset Pompe disease) patients aged 16 to 78 naïve to enzyme replacement therapy were treated either with 20 mg/kg of Nexviadyme (n=51) or 20 mg/kg of alglucosidase alfa (n=49). During the double-blind active-controlled period of 49 weeks, serious adverse reactions were reported in 2% of patients treated with Nexviadyme 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 Nexviadyme group permanently discontinued the treatment. The most frequently reported ADRs (>5%) in patients treated with Nexviadyme were headache, nausea, pruritus, urticaria, and fatigue.

The 95 patients who entered open-label extension period of EFC14028/COMET consisted of 51 patients who continued treatment with Nexviadyme and 44 patients who switched from alglucosidase alfa to Nexviadyme.

During the open-label extension period, serious adverse reactions were reported by 3 (5.8%) patients continuing Nexviadyme treatment throughout the study and by 3 (6.8%) patients who switched to Nexviadyme. The most frequently reported adverse reactions (>5%) by patients continuing Nexviadyme treatment throughout the study were nausea, chills, erythema, pruritus, and urticaria. The most frequently reported adverse reactions (>5%) by patients who switched to Nexviadyme were pruritus, rash, headache, nausea, chills, fatigue, and urticaria.

No adverse reaction or IAR was reported by the additional paediatric patient directly enrolled in the open-label extension period.

Description of selected adverse reactions

Hypersensitivity (including anaphylaxis)
In a pooled safety analysis, 86/142 (60.6%) patients experienced hypersensitivity reactions including 7/142 (4.9%) patients who reported severe hypersensitivity reactions and 4/142 (2.8%) patients who experienced anaphylaxis. Some of the hypersensitivity reactions were IgE mediated. Anaphylaxis signs and symptoms included tongue oedema, hypotension, hypoxia, respiratory distress, chest pressure, generalised oedema, generalised flushing, feeling hot, cough, dizziness, dysarthria, throat tightness, dysphagia, 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 tongue oedema, respiratory failure, respiratory distress, generalized oedema, erythema, urticaria, and rash.

Infusion-associated reactions (IARs)
In a pooled safety analysis, IARs were reported in approximately 56/142 (39.4%) of patients treated with avalglucosidase alfa in clinical studies. Severe IARs were reported in 6/142 (4.2%) of patients including symptoms of respiratory distress, hypoxia, chest discomfort, generalized oedema, tongue oedema, dysphagia, nausea, erythema, urticaria, and increased or decreased blood pressure. IARs reported in more than 1 patient included respiratory distress, chest discomfort, dyspnoea, cough, oxygen saturation decreased, throat irritation, dyspepsia, nausea, vomiting, diarrhoea, lip swelling, swollen tongue, erythema, palmar erythema, rash, rash erythematous, pruritus, urticaria, hyperhidrosis, skin plaque, ocular hyperaemia, eyelid oedema, face oedema, increased or decreased blood pressure, tachycardia, headache, dizziness, tremor, burning sensation, pain (including pain in extremity, abdominal pain upper, oropharyngeal pain, and flank pain), somnolence, sluggishness, fatigue, pyrexia, influenza like illness, chills, flushing, feeling hot or cold, cyanosis, and pallor. 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 treatment-emergent IARs (>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.

During the open-label extension period, IARs were reported in 12 (23.5%) patients continuing Nexviadyme treatment throughout the study; IARs reported in more than 1 patient were nausea, chills, erythema, pruritus, pyrexia, urticaria, rash, and ocular hyperaemia. IARs were reported in 22 (50%) patients who switched to Nexviadyme; IARs reported in more than 1 patient were pruritus, headache, rash, nausea, chills, fatigue, urticaria, respiratory distress, feeling cold, chest discomfort, erythema,

rash erythematous, rash pruritic, skin plaque, burning sensation, lip swelling, and swollen tongue. The number of IARs in both groups decreased over time.

Immunogenicity
The incidence of ADA response to avalglucosidase alfa in Nexviadyme-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 IARs was observed in both ADA-positive and ADA-negative patients. Increase in the incidence of IARs 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 (69.2%) reported in the high ADA peak titre range ≥12,800, compared with an incidence of 33.3% in patients with intermediate ADA titre 1,600-6,400, an incidence of 14.3% 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 2 treatment-experienced patients developed anaphylaxis. The occurrences of IARs were similar between paediatric patients with ADA positive and negative status. One treatment-experienced paediatric patient developed anaphylaxis (see section 4.4).

In clinical study EFC14028/COMET, 81 of 96 (84.4%) patients developed treatment-emergent ADA. Majority of patients developed ADA titre in the low to intermediate range, with 7 patients reported High Sustained Antibody Titres (HSAT) to Nexviadyme. Evaluation of ADA cross-reactivity at week 49 showed that patients generate antibodies that are cross-reactive to alglucosidase alfa and Nexviadyme were detected in 3 (5.9%) patients. Variable impact on PK, PD, and efficacy measures were observed among high titre patients, however, in most patients there was no clinically significant effect of ADA on efficacy (see section 5.2).

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

	Nexviadyme			
	Treatment-naïve patients Avalglucosidase alfa ADA[a]	**Treatment-experienced patients[b] Avalglucosidase 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**
	(N=62) N (%)	**(N=58) N (%)**	**(N=6) N (%)**	**(N=16) N (%)**
ADA at baseline	2 (3.3)	43 (74.1)	1 (16.7)	2 (12.5)
Treatment emergent ADA	59 (95.2)	36 (62.1)	1 (16.6)	9 (56.3)
Neutralizing antibody				
Both NAb types	14 (22.6)	5 (8.6)	0	0
Inhibition enzyme activity, only	5 (8.1)	6 (10.3)	0	0
Inhibition of enzyme uptake, only	12 (19.4)	15 (25.9)	0	2 (12.5%)

[a] Includes two paediatric patients
[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 0.6-11.8 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 two paediatric patients (9 and 16 years old) with LOPD) were similar to those reported in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.*

4.9 Overdose

Excessive infusion rate of Nexviadyme 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 identifies 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: Alimentary tract and metabolism products - enzymes, ATC code: A16AB22.

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 Nexviadyme 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 Nexviadyme or alglucosidase alfa once every other week for 12 months (49 weeks).

Study 1 included an open-label extension treatment period where all patients in the alglucosidase alfa arm were switched to Nexviadyme and continued treatment up to at least week 145. Overall, 95 patients entered the open-label period (51 from the Nexviadyme arm and 44 from the alglucosidase alfa arm). An additional paediatric patient was enrolled directly into the extension treatment period with Nexviadyme.

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 Nexviadyme 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

Nexviadyme 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.

For patients who switched from alglucosidase alfa to Nexviadyme treatment after week 49, the LS mean change in FVC % predicted from week 49 to week 145 was 0.81 (1.08) (95% CI: -1.32, 2.95). A stabilization in FVC % predicted was maintained after the switch to Nexviadyme in the alglucosidase alfa group with similar values to the Nexviadyme group at week 145. Patients who continued in the Nexviadyme arm maintained an improvement in FVC % predicted compared with baseline.

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

		Nexviadyme (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 Estimated change from baseline to week 49 (MMRM)	Mean (SD)	65.49 (17.42)	61.16 (13.49)
	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 Nexviadyme 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 Nexviadyme compared with alglucosidase alfa. The results for the 6MWT are detailed in Table 5.

For patients who switched from alglucosidase alfa to Nexviadyme treatment after week 49, the LS mean change in 6MWT (distance walked in meters) from week 49 to week 145 was -2.3 m (10.6), 95% CI: -23.2, 18.7. At Week 145, a stabilization in 6MWT was observed after the switch from the alglucosidase alfa group to Nexviadyme. The Nexviadyme arm participants sustained the improvement compared with baseline.

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, who started on Nexviadyme 20 mg/kg every other week, the mean percentage (SD) change in urinary hexose tetrasaccharides from baseline to week 49 was -53.90% (24.03), which was maintained at week 145 at -53.35% (72.73) in patients who continued treatment with Nexviadyme. In patients who started on alglucosidase alfa 20 mg/kg every other week, the mean percentage (SD) change in urinary hexose tetrasaccharides from baseline to week 49 was -10.8% (32.33), further decreased to -48.04% (41.97) at week 145 after switching from alglucosidase alfa to Nexviadyme.

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

Endpoint	Nexviadyme 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]	8.71 (2.09)	4.33 (2.19)	4.38 (-1.64, 10.39)
Maximum Expiratory Pressure (% predicted)[c]	10.97 (2.84)	8.35 (2.97)	2.61 (-5.61, 10.83)
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)

[a] The 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.

[b] LS 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.

[c] Post-hoc sensitivity analysis excluding 4 patients (2 in each treatment arm) with supraphysiologic baseline MIP and MEP values.

[d] Physical Component Summary.

[e] Mental Component Summary.

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 Nexviadyme 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 Nexviadyme 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 Nexviadyme. The secondary objective was to determine the efficacy of Nexviadyme. 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 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 Nexviadyme 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 Nexviadyme 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 Nexviadyme at 20 mg/kg every other week, mean (SD) percentage change was 0.34% (42.09).

The long-term effects of treatment with Nexviadyme 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 Nexviadyme (see section 4.2 and 4.8) and two paediatric patients aged 9 and 16 years with LOPD was treated with Nexviadyme.

The European Medicines Agency has deferred the obligation to submit the results of studies with Nexviadyme in one or more subsets of the paediatric population for the treatment of Pompe disease (see section 4.2 for information on paediatric use).

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 Cmax and mean AUC2W 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 Cmax 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 AUC2W 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.

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, 95.2% (59 of 62 patients) receiving Nexviadyme developed treatment-emergent ADA. Given the variability in ADA response, no clear trend of ADA peak titre and impact on PK was evident in patients at week 49.

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 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 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.
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 Nexviadyme. After the infusion is complete, the intravenous line should be flushed with glucose 5% in water.
10. Nexviadyme should not be infused in the same intravenous line with other medicinal products.

Table 6 – Projected intravenous infusion volumes for Nexviadyme 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.

7. MARKETING AUTHORISATION HOLDER

Sanofi B.V.
Paasheuvelweg 25
1105 BP Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1579/001
EU/1/21/1579/002
EU/1/21/1579/003
EU/1/21/1579/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 June 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Genzyme Flanders,
Cipalstraat 8,
2440 Geel, Belgium

Name and address of the manufacturers responsible for batch release

Genzyme Ireland Limited,
IDA Industrial Park,
Old Kilmeaden Road,
Waterford, Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this medicinal product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Nexviadyme in each Member State, the Marketing Authorization Holder (MAH) must agree about the content and format of the educational program, including communication media, distribution modalities, and any other aspects of the program, with the National Competent Authority. The educational program is aimed at increasing the awareness

about the immunosurveillance service and to support the correct and safe administration of the product in the home setting.

The MAH shall ensure that in each member state where Nexviadyme is marketed, all healthcare professionals (HCPs) who are expected to prescribe, dispense, and administer Nexviadyme are provided with the following educational package to be disseminated through professional bodies:

- Healthcare professionals (HCPs) guide for immunosurveillance service and
- Home infusion guide for HCPs

Guide for healthcare professionals for Immunosurveillance Service shall include the following key elements:

- Testing recommendations:
  - Baseline serum sample collection prior to the first infusion is strongly encouraged.
  - Immunoglobulin G (IgG) antibody titres should be regularly monitored and IgG anti-drug antibody (ADA) testing should be considered if patients do not respond to therapy.
  - Treated patients may be tested for inhibitory antibodies if they experience a decrease in clinical benefit despite continued treatment with Nexviadyme.
  - Adverse-event-driven immunologic testing, including IgG and Immunoglobulin E (IgE) ADA, should be considered for patients at risk for allergic reaction or previous anaphylactic reaction to Myozyme (alglucosidase alfa).
  - Adverse-event-driven immunologic testing should also be considered in patients who experience moderate/severe or recurrent infusion-associated reactions (IARs) suggestive of hypersensitivity reactions, anaphylactic reactions.
- Testing practicalities of the testing service and contact details
  - Description of the testing services: available tests, indication for testing, sample type, Frequency of testing, collection time
  - Procedure for testing: diagram summarizing main steps for HCP requesting Specialty testing services

The home infusion guide for HCPs which will serve as training document to HCPs who will perform the infusion at home shall contain the following key elements:

- Requirements and organization of the home infusion including equipment, pre‑treatment and emergency treatments.
- Details on the preparation and administration of Nexviadyme, including all the steps of preparation, reconstitution, dilution, and administration
- Medical evaluation of the patient prior to administration of the infusion at home
- Information on signs and symptoms related to infusion-associated reactions and recommended actions for the management of the ADRs when symptoms occur.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nexviadyme 100 mg powder for concentrate for solution for infusion
avalglucosidase alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 100 mg of avalglucosidase alfa.

3. LIST OF EXCIPIENTS

Histidine
Histidine hydrochloride monohydrate
Glycine
Mannitol
Polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion

1 vial
5 vials
10 vials
25 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after reconstitution and dilution.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use immediately after dilution.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi B.V.
Paasheuvelweg 25
1105 BP Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1579/001 1 vial
EU/1/21/1579/002 5 vials
EU/1/21/1579/003 10 vials
EU/1/21/1579/004 25 vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Nexviadyme 100 mg powder for concentrate
avalglucosidase alfa
IV use after reconstitution and dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 mg

6. OTHER

Sanofi B.V.-NL

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Nexviadyme 100 mg powder for concentrate for solution for infusion
avalglucosidase alfa

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist. or nurse.
- If you get any side effects, talk to your doctor, pharmacist. or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Nexviadyme is and what it is used for

What Nexviadyme is
Nexviadyme contains an enzyme called avalglucosidase alfa – it is a copy of the natural enzyme called acid alpha-glucosidase (GAA) that is lacking in people with Pompe disease.

What Nexviadyme is used for
Nexviadyme is used to treat people of all ages who have Pompe disease.

People with Pompe disease have low levels of the enzyme acid alpha-glucosidase (GAA). This enzyme helps control levels of glycogen (a type of carbohydrate) in the body. Glycogen provides the body with energy, but in Pompe disease high levels of glycogen build up in different muscles and damages them. The medicine replaces the missing enzyme so that the body can reduce the build-up of glycogen.

2. What you need to know before you are given Nexviadyme

Do not use Nexviadyme
If you have had life-threatening allergic (hypersensitive) reactions to avalglucosidase alfa or any of the other ingredients of this medicine (listed in section 6) and these reactions occurred again after stopping and restarting the medicine.

Warnings and precautions
Talk to your doctor or pharmacist or nurse before using Nexviadyme

Speak to your doctor immediately if treatment with Nexviadyme causes:
- allergic reactions, including anaphylaxis (a severe allergic reaction) – see under ‘Possible side effects’, below for symptoms
- infusion-associated reaction while you are receiving the medicine or in the few hours afterwards – see under ‘Possible side effects’, below for symptoms

Also tell your doctor if you have swelling in your legs or widespread swelling of your body. Your doctor will decide if your Nexviadyme infusion should stop and the doctor will give you appropriate medical treatment. Your doctor will also decide if you can continue receiving avalglucosidase alfa.

Other medicines and Nexviadyme
Tell your doctor or pharmacist if you are using, have recently used, or might use any other medicines.

Pregnancy and breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine. There is no information about the use of Nexviadyme in pregnant women. You must not receive Nexviadyme during pregnancy unless your doctor specifically recommends it. You and your doctor should decide if you can use Nexviadyme if you are breast-feeding.

Driving and using machines
Nexviadyme may have a minor effect on the ability to drive and use machines. Because dizziness, low blood pressure and sleepiness can occur as infusion-associated reactions, this may affect the ability to drive and use machines on the day of the infusion.

3. How Nexviadyme is given

Nexviadyme will be given to you under the supervision of a health care professional who is experienced in the treatment of Pompe disease.

You may be given other medicines before you receive Nexviadyme, to reduce some side effects. Such medicines include an antihistamine, a steroid and a medicine (such as paracetamol) to reduce fever.

The dose of Nexviadyme is based on your weight and will be given to you once every 2 weeks.

- The recommended dose of Nexviadyme is 20 mg/kg of body weight.

Home infusion
Your doctor may consider that you can have home infusion of Nexviadyme if it is safe and convenient to do so. If you get any side effects during an infusion of Nexviadyme, your home infusion staff member may stop the infusion and start appropriate medical treatment.

Instructions for proper use
Nexviadyme is given through a drip into a vein (intravenous infusion). It is supplied to the healthcare professional as a powder to mix with sterile water and further dilute with glucose before infusing it.

If you are given more Nexviadyme than you should
Excessive infusion rate of Nexviadyme may result in hot flush.

If you miss your dose of Nexviadyme
If you have missed an infusion, please contact your doctor. If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or nurse.

If you stop using Nexviadyme
Speak to your doctor if you wish to stop Nexviadyme treatment. The symptoms of your disease may worsen if you stop treatment.

4. Possible side effects

Side effects mainly occur while patients are being given Nexviadyme infusion or shortly afterwards. You must tell your doctor immediately if you get an infusion-associated reaction or an allergic reaction. Your doctor may give you medicines before your infusion to prevent these reactions.

Infusion-associated reactions
Mostly infusion-associated reactions are mild or moderate. Symptoms of infusion-associated reaction include chest discomfort, increased blood pressure, increased heart rate, chills, cough, diarrhoea, fatigue, headache, flu-like illness, nausea, vomiting, red eye, pain in arms and legs, skin redness, itchy skin, rash, and hives.

Allergic reactions
Allergic reactions may include symptoms such as difficulty breathing, chest pressure, flushing, cough, dizziness, nausea, redness on palms and feet, itchy palms and feet, swollen lower lip and tongue, low level of oxygen in the blood, and rash.

Very Common (may affect more than 1 in 10 people)
- Hypersensitivity
- Headache
- Nausea
- Itchy skin
- Rash

Common (may affect up to 1 in 10 people)
- Anaphylaxis (severe allergic reaction)
- Dizziness
- Sleepiness
- Tremor (shaking)
- Burning sensation
- Red eyes
- Itchy eyes
- Swelling of eyelid
- Rapid heartbeat
- Flushing
- Raised blood pressure
- Low blood pressure
- Skin and lips turning blue
- Hot flush
- Pale skin
- Cough
- Difficulty breathing
- Throat irritation
- Mouth and throat pain
- Diarrhoea
- Vomiting
- Lip swelling
- Swollen tongue
- Abdominal (belly) pain
- Abdominal (belly) pain upper
- Indigestion
- Hives
- Redness of hands
- Redness of skin
- Red rash

- Excessive sweating
- Itchy rash
- Skin plaque
- Muscle spasms
- Muscle aches
- Pain in arm or leg
- Flank pain
- Fatigue
- Chills
- Fever
- Chest discomfort
- Pain
- Flu-like illness
- Infusion site pain
- Low blood oxygen
- Weakness
- Swelling of face
- Feeling cold or hot

Uncommon (may affect up to 1 in 100 people)
- Inflammation of eyes
- Numbness or tingling
- Watery eyes
- Extra heart beats
- Rapid breathing
- Swelling of throat
- Numbness in the mouth, tongue, or lip
- Tingling in the mouth, tongue, or lip
- Difficulty swallowing
- Swelling of skin
- Skin discolouration
- Facial pain
- Increased body temperature
- Infusion site tissue leakage
- Infusion site joint pain
- Infusion site rash
- Infusion site reaction
- Infusion site itching
- Localised oedema
- Swelling in the arms and legs
- Breath sounds abnormal (wheezing)
- Blood test for inflammation
- Reduced sensation to touch, pain, and temperature
- Oral discomfort (including lip burning sensation)

The reported side effects seen in children and adolescents were similar to those seen in adults.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine

5. How to store Nexviadyme

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

Unopened vials:
Store in a refrigerator (2°C - 8°C).

Reconstituted solution:
After reconstitution, immediate use for dilution is recommended. The reconstituted solution can be stored up to 24 hours when refrigerated at 2°C to 8°C.

Diluted solution:
After dilution, immediate use is recommended. The diluted solution can be stored for 24 hours at 2°C to 8°C followed by 9 hours at room temperature (up to 25°C).

Do not throw away any medicines via wastewater or household waste. Ask your doctor, pharmacist, or nurse how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Nexviadyme contains
The active substance is avalglucosidase alfa. One vial contains 100 mg of avalglucosidase alfa. After reconstitution, the solution contains 10 mg of avalglucosidase alfa per ml and after dilution the concentration varies from 0.5 mg/ml to 4 mg/ml.
The other ingredients are

- Histidine
- Histidine hydrochloride monohydrate
- Glycine
- Mannitol
- Polysorbate 80

What Nexviadyme looks like and contents of the pack
Avalglucosidase alfa is a powder for concentrate for solution for infusion in a vial (100 mg/vial). Each pack contains 1, 5, 10, or 25 vials. Not all pack sizes may be marketed.

The powder is white to pale yellow. After reconstitution it is a clear, colourless to pale yellow solution. The reconstituted solution must be further diluted.

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Manufacturer
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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

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The following information is intended for healthcare professionals only:

Reconstitution

Use aseptic technique during reconstitution.

1. Determine the number of vials to be reconstituted based on the 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 water for injections (WFI) to each vial. Each vial will yield 100 mg/10 ml (10 mg/ml). Avoid forceful impact of the WFI on the powder and avoid foaming. This is done by slow drop-wise addition of the water for injection down the inside of the vial and not directly onto the lyophilised powder. Tilt and roll each vial gently. Do not invert, swirl, or shake.
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 discoloured, do not use. Allow the solution to become dissolved.

Dilution

1. 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 1 for the recommended total infusion volume based on the patient weight.
2. Slowly withdraw the volume of reconstituted solution from each vial (calculated according to the patient's weight).
3. Add the reconstituted solution slowly and directly into the 5% glucose solution. Avoid foaming or agitation of the infusion bag. Avoid air introduction into the infusion bag.
4. Gently invert or massage the infusion bag to mix. Do not shake.
5. 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 Nexviadyme. After the infusion is complete, flush the intravenous line with glucose 5% in water.
6. Do not infuse Nexviadyme in the same intravenous line with other medicines.

Table 1: Projected Intravenous Infusion Volumes for Nexviadyme Administration by Patient Weight at 20 mg/kg and 40 mg/kg Dose

Patient Weight Range (kg)	Total infusion volume (ml) for 20 mg/kg	Total infusion volume (ml) for 40 mg/kg
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 medicine or waste material should be disposed of in accordance with local requirements.

Home infusion

Infusion of Nexviadyme 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 Nexviadyme 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. 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.