Date: 12 January 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Nexviadyme

International non-proprietary name: avalglucosidase alfa
Pharmaceutical form: powder for concentrate for solution for infusion
Dosage strength: 100 mg
Route(s) of administration: intravenous use
Marketing Authorisation Holder: Sanofi-Aventis (Suisse) SA
Marketing Authorisation No.: 67871
Decision and Decision date: approved on 17 November 2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
CIMPR	Cation-independent M6P receptor
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
EFD	Embryo-foetal development
ERA	Environmental Risk Assessment
GAAKO	Acid α-glucosidase (GAA) knockout mice
GD	Gestation day
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
IOPD	Infantile-onset Pompe disease
IV	Intravenous
LOPD	Late-onset Pompe disease
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PND	Postnatal day
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance avalglucosidase alfa of the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 2 of the TPA. Orphan Drug Status was granted on 25 March 2020.

Worksharing procedure
The applicant requested a worksharing procedure with Australia, Canada and Switzerland.
The ACCESS NAS (New Active Substance) worksharing initiative is a collaboration between regulatory authorities – Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA), the UK's Medicines & Healthcare products Regulatory Agency (MHRA), Swissmedic – and the pharmaceutical industry.
The worksharing initiative coordinates the assessment of a NAS application that has been filed in at least two jurisdictions.

For aspects of the evaluation not covered in this SwissPAR, please refer to the publicly available assessment reports for Nexviadyme issued by the regulatory authorities HC and TGA (see https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/summary-basis-decision.html and https://www.tga.gov.au/ws-auspar-index.

2.2 Indication and Dosage

2.2.1 Requested Indication

Nexviadyme (avalglucosidase alfa) is indicated for long-term enzyme replacement therapy for the treatment of patients with late-onset Pompe's disease (LOPD) (acid α-glucosidase deficiency).

2.2.2 Approved Indication

Nexviadyme (avalglucosidase alfa) is indicated for long-term enzyme replacement therapy for the treatment of patients with late-onset Pompe's disease (LOPD) (acid α-glucosidase deficiency).

2.2.3 Requested Dosage

The recommended dose is 20 mg/kg body weight administered every other week.

2.2.4 Approved Dosage

(see appendix)

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2.3 Regulatory History (Milestones)

Application	21 October 2020
Formal control completed	30 November 2020
List of Questions (LoQ)	30 March 2021
Answers to LoQ	27 May 2021
Predecision	21 July 2021
Answers to Predecision	20 August 2021
Labelling corrections	7 October 2021
Answers to Labelling corrections:	20 October 2021
Final Decision	17 November 2021
Decision	approval

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3 Quality Aspects

Swissmedic has not assessed the primary data relating to quality aspects of this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's Request(s) / Worksharing procedure).

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4 Nonclinical Aspects

The applicant submitted a comprehensive set of nonclinical studies based on relevant ICH guidelines. The applicant also considered the FDA/CDER's draft guidance document on nonclinical assessment for enzyme replacement therapy products. The pivotal toxicology studies were conducted in compliance with GLP.

Pharmacology

Avalglucosidase alfa should decrease lysosomal glycogen more efficiently than the unmodified enzyme (alglucosidase alfa, Myozyme®) via interaction of the bis-mannose-6-phosphate (M6P) moieties on the enzyme with the cation-independent M6P receptor (CIMPR). This mechanism is supported by *in vitro* studies that showed higher affinity of avalglucosidase alfa to CIMPR and increased uptake and processing in human Pompe fibroblasts when compared to alglucosidase alfa. *In vivo* pharmacology studies in a model of Pompe disease (acid α-glucosidase (GAA) knockout mice, GAAKO) showed that the administration of avalglucosidase alfa at 12 and 20 mg/kg reduced glycogen levels in relevant tissues, including heart, skeletal muscle, and diaphragm. The lowest dose of 4 mg/kg also showed efficacy in the heart but not in the other tissues. The *in vivo* potency of avalglucosidase alfa to reduce glycogen levels was about 3 to 5-fold higher compared to alglucosidase alfa. Based on additional *in vivo* studies in GAAKO mice, three glycans (each containing two M6P moieties) per mole are sufficient to achieve the higher potency.
Repeated administration of avalglucosidase alfa or alglucosidase alfa to GAAKO mice was associated with hypersensitivity reactions including mortality. Hypersensitivity / infusion-related reactions are a known risk with Myozyme® therapy and were also observed in the clinical studies with avalglucosidase alfa.
No secondary pharmacodynamics or pharmacodynamic drug interaction studies were conducted with avalglucosidase alfa, which is accepted given that it is an enzyme replacement therapy.
No dedicated safety pharmacology studies were conducted. Cardiovascular, respiratory and central nervous system evaluations were included in the 26-week toxicity study in monkeys. There were no effects on the respective parameters.

Pharmacokinetics

The applicant investigated the pharmacokinetics (PK) of avalglucosidase alfa following IV administration in GAAKO mice and in the animal species used for safety evaluation (i.e. CD-1 mice, cynomolgus monkeys, and rabbits). Overall, the PK profiles in the animal species were comparable with the PK in humans. Saturation kinetics occurred in mice and monkeys at ≥40 mg/kg.
In GAAKO mice, serum AUC, $t_{1/2}$, and volume of distribution of avalglucosidase alfa were significantly lower than those of alglucosidase alfa. This is probably related to increased tissue uptake of the modified enzyme (see *Pharmacology*).
The distribution of avalglucosidase alfa to selected tissues was studied in GAAKO mice following single IV administration at 20 mg/kg; tissue levels were determined using an enzyme activity assay. About 38-82% of the dose was detected in the liver, whereas much lower concentrations (≤ 0.4%) were detected in the heart and skeletal muscle. Avalglucosidase alfa tissue levels were in general comparable to those measured after administration of 20 mg/kg alglucosidase alfa. In the heart, avalglucosidase alfa tissue levels were higher than those for alglucosidase alfa at 6 and 24 h post dose, which correlates with the higher potency observed in the pharmacology studies. Treatment of pregnant CD-1 mice with avalglucosidase alfa did not lead to increased foetal liver concentrations, indicating little or no enzyme transfer across the placental barrier. This is in line with the results of previous studies conducted with alglucosidase alfa.
Conventional nonclinical studies on the metabolism and excretion of avalglucosidase alfa were not conducted due to the protein structure of the compound, in line with ICH S6(R1).
Avalglucosidase alfa was immunogenic in mice and monkeys. ADAs generally occurred in all animals used for evaluation, but the presence of ADAs had no effect on drug exposure.

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Toxicology
Toxicity studies for avalglucosidase alfa were conducted in CD-1 mice, cynomolgus monkeys and female rabbits. Due to hypersensitivity reactions (including mortality) in mice, monkeys were the only species used for chronic toxicity testing. The clinical route of administration (IV) was used (mice: bolus injection; rabbits: 10 min infusion; monkeys: 6 h infusion). In studies up to 28 days, dosing was once weekly or more frequently. In studies with longer treatment periods, test item administration was every other week, in line with the proposed for clinical use. The vehicle corresponded to the proposed clinical formulation. Diphenhydramine (DPH) was administered in some of the studies in mice to prevent or reduce hypersensitivity reactions.
Repeated-dose toxicity in mice was assessed in two non-GLP studies, a 14-day study with up to 50 mg/kg every other day and a 28-day study with up to 120 mg/kg once weekly (cumulative (2-week) exposure 7.4-fold the mean AUC_{2w} in LOPD patients). In monkeys, repeated-dose toxicity studies consisted of a non-GLP 28-day study, a 26-week GLP study, and a 13-week GLP study to qualify residual glycan levels. With the exception of signs of hypersensitivity in the 28-day mouse study and the 13-week monkey study, the animals tolerated the treatment with avalglucosidase alfa well and no target organs were identified. However, only a small number of animals was used for toxicity assessment in the 28-day study in mice (3/sex/group). In the pivotal toxicity study (26-week study in monkeys), lower heart weights were recorded in males and females at both dose levels of avalglucosidase alfa (50 and 200 mg/kg every other week). These findings might be related to the pharmacological action of avalglucosidase alfa (reduction of glycogen content), although there were no corresponding microscopic findings. Mean exposure at the NOAEL of 200 mg/kg in monkeys was approx. 23-fold the mean AUC_{2w} in LOPD patients.
No conventional genotoxicity and carcinogenicity studies with avalglucosidase alfa were conducted, with reference to ICH S6(R1). The applicant submitted several studies that aimed to investigate the genotoxic properties of avalglucosidase alfa, the glycan moiety, and/or the glycan linker. This included an exploratory (non-GLP) micronucleus study in GAAKO mice with 50 mg/kg avalglucosidase alfa. No increase in micronucleated reticulocytes or normochromatic erythrocytes vs. the vehicle control group was observed. The distribution of avalglucosidase alfa to bone marrow was confirmed by enzyme activity measurements. The glycan moiety tested negative in *in vitro* GLP-compliant studies for genotoxicity (bacterial reverse mutation test and chromosome aberration test in cultured human peripheral blood lymphocytes). Furthermore, the applicant assessed the risk of formation of hydrazine-containing compounds by degradation of avalglucosidase alfa in studies with human hepatocytes and plasma. The results of these investigations do not raise concerns regarding the genotoxicity of the glycan moiety of avalglucosidase alfa. The applicant also provided a carcinogenicity risk assessment for avalglucosidase alfa based on the results of the nonclinical studies, literature searches, and data review for the marketed alglucosidase alfa products. Based on the weight of evidence, the carcinogenic potential of avalglucosidase alfa is considered low.
The reproductive and developmental toxicity of avalglucosidase alfa were assessed in GLP-compliant studies in mice and rabbits. Treatment of mice with up to 50 mg/kg every other day had no effects on fertility parameters. In a study on embryo-foetal development (EFD) in mice, increased post-implantation occurred at the high dose level (50 mg/kg/day from gestation day (GD) 6 to GD 15; cumulative exposure 17-fold the mean AUC_{2w} in LOPD patients). This dose was also associated with maternal toxicity (mortality in two animals, which was probably related to immunologic response). There were no effects on foetal sex ratio or weight, and there were no avalglucosidase alfa-related malformations or variations. At the NOAEL for embryo-foetal development (20 mg/kg), the cumulative plasma exposure of maternal animals was 4.8-fold the mean AUC_{2w} in LOPD patients. The increased post-implantation loss at 50 mg/kg was considered related to the maternal toxicity rather than a direct embryotoxic effect of avalglucosidase alfa. This is supported by the lack of tissue distribution via the placental barrier. In the EFD study in rabbits, no effects on embryo-fetal viability and development were observed with administration of avalglucosidase alfa (up to 100 mg/kg/day on GDs 6-19). Cumulative exposure of maternal animals at the NOAEL (100 mg/kg/day) was 91-fold the mean AUC_{2w} in LOPD patients. In a study on pre- and postnatal development in mice, no effects on gestation performance or survival and development of the offspring were observed up to the highest

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dose level (50 mg/kg every other day). In conclusion, there is no particular concern with regard to the reproductive/developmental toxicity of avalglucosidase alfa, but a risk to the fetus due to hypersensitivity reactions in the mother cannot be excluded. This is adequately reflected in the information for healthcare professionals.
Avalglucosidase alfa was assessed in a toxicity study in juvenile mice with treatment from postnatal day (PND) 21 to PND 77 or 91 (up to 100 mg/kg every other week), followed by a 4-week non-dosing period. Mortality and clinical signs associated with immunologic response occurred at all dose levels, but there were no effects on growth and development (including sexual maturation, learning and behaviour, and reproductive function). Exposure at the 100 mg/kg dose was 2.1 to 3.7-fold the highest mean AUC_{2w} in infantile-onset Pompe disease (IOPD) patients. Notably, the study does not support risk assessment for paediatric patients younger than 2 years of age since treatment started at PND 21.
The applicant conducted additional studies to qualify impurities. The controls for impurities are considered adequate.
The description and evaluation of the nonclinical safety data in the RMP are acceptable.
Due to the protein nature of avalglucosidase alfa, no experimental studies for ecotoxicity are required.

Nonclinical conclusions
Overall, the nonclinical studies are considered sufficient to support the approval of avalglucosidase alfa in the proposed indication. Hypersensitivity reactions observed in mice and monkeys are a known risk for the unmodified enzyme (alglucosidase alfa, Myozyme®), and signs of hypersensitivity reactions were also seen in clinical studies with avalglucosidase alfa. All relevant nonclinical data are stated in the information for healthcare professionals.

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5 Clinical and Clinical Pharmacology Aspects

Swissmedic has not assessed the primary data relating to clinical aspects of this application and, for late-onset Pompe disease (LOPD), is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's Request / Worksharing procedure).

5.1 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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7 Appendix

7.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Nexviadyme, powder for concentrate for solution for infusion, was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow for quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Nexviadyme 100 mg, powder for concentrate for solution for infusion

Composition

Active substances

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

Excipients

L-Histidine, L-histidine hydrochloride monohydrate, glycine, mannitol, polysorbate 80.

Pharmaceutical form and active substance quantity per unit

Powder for concentrate for solution for infusion
White to pale yellow lyophilized powder

Each single-use vial contains 100 mg avalglucosidase alfa.
After reconstitution, the solution contains 10 mg avalglucosidase alfa per mL. After reconstitution, each vial contains 10.3 mL of reconstituted solution and a total extractable volume of 10.0 mL at 10 mg/mL of Nexviadyme. Each vial contains an overflow to compensate for the loss of liquid during preparation. This overfill ensures that after dilution with the entire contents, there is a solution containing 10 mg/mL of Nexviadyme.

Indications/Uses

Nexviadyme (avalglucosidase alfa) is indicated for long-term enzyme replacement therapy for the treatment of patients with late-onset Pompe's disease (LOPD) (acid α-glucosidase deficiency).

Dosage/Administration

Treatment with Nexviadyme should be supervised by a physician experienced in the management of patients with Pompe's disease or other metabolic or inherited neuromuscular disorders.

Dosage

The recommended dose of Nexviadyme is 20 mg/kg body weight given every other week.

For each treatment, the trade name and batch number should be recorded for the purposes of biotechnology medicinal product traceability.

Patients with pre-existing liver failure

The safety and efficacy of Nexviadyme have not been studied in patients with liver failure.
It is therefore not possible to make a specific dosing recommendation for these patients.

Patients with impaired renal function

No dose adjustment is necessary in patients with mildly impaired renal function.
Nexviadyme has not been studied in patients with moderate or serious renal impairment. It is therefore not possible to make a specific dosing recommendation for patients with moderate to severe renal impairment.

Elderly patients

Clinical studies on Nexviadyme included 14 patients aged 65 to 75 years and 3 patients over 75 years. No dosage adjustment is recommended for patients over 65 years of age.

Children and adolescents

There are limited data from clinical studies on patients with late-onset Pompe's disease (LOPD); 1 patient aged 16 years was treated with Nexviadyme.

Mode of administration

Nexviadyme should be administered by intravenous infusion. For instructions on reconstitution and dilution of the drug before administration, see the "*Instructions for handling*" section.

The infusion should be administered gradually, depending on the patient's response and comfort, over approximately 4 hours. It is recommended that the infusion be started at an initial rate of 1 mg/kg/hour and gradually increased by 2 mg/kg/hour every 30 minutes if there are no signs of infusion-related reactions (IRR), until a maximum rate of 7 mg/kg/hour is reached. Vital signs should be monitored at each step before increasing the infusion rate. Patients may be pre-treated with antihistamines, antipyretics and/or corticosteroids to prevent or reduce allergic reactions.

Allergic reactions, including anaphylaxis, hypersensitivity reactions, and infusion-related reactions may occur with the administration of Nexviadyme (see "*Warnings and precautions*" section and "*Undesirable effects*" section).
If anaphylaxis or severe hypersensitivity or infusion-related reactions (IRR) occur, discontinue Nexviadyme immediately and initiate appropriate medical treatment. In the event of mild to moderate hypersensitivity or IRR reactions, the infusion rate may be slowed or temporarily stopped and/or appropriate medical treatment may be instituted. Symptoms may persist despite discontinuation of Nexviadyme.

Re-exposure after discontinuation of Nexviadyme
If Nexviadyme administration has been discontinued due to adverse reactions as described above, cautious re-exposure may be considered after careful clinical evaluation. However, experience from clinical practice with re-exposure is limited. It should be kept in mind that adverse reactions such as those described above, including serious developments, may recur even with re-exposure at a reduced dose.
If re-exposure is contemplated, wait for at least 30 minutes after symptoms have resolved. Nexviadyme should then be restarted under close patient supervision at a maximum dose of half the dose at which symptoms first occurred. Depending on the patient's clinical response, the dose may then be increased again slowly and at the discretion of the treating physician.

Contraindications

Hypersensitivity to the active substance or to any of the life-threatening excipients when re-infusion has failed (see the "*Warnings and precautions*" section).

Warnings and precautions

Traceability
To improve the traceability of biological drugs, the name and lot number of the administered product must be clearly recorded.

Serious hypersensitivity reactions, including anaphylaxis

Hypersensitivity reactions, including anaphylaxis, have been reported in patients treated with Nexviadyme (see the "*Description of certain undesirable effects*" section).

Appropriate medical assistance, including cardiopulmonary resuscitation equipment, especially for patients with cardiac hypertrophy and patients with severely impaired respiratory function, should be readily available when Nexviadyme is administered.

If severe hypersensitivity or anaphylaxis occurs, Nexviadyme should be discontinued immediately and appropriate medical treatment instituted. The risks and benefits of resuming Nexviadyme after a severe anaphylactic or hypersensitivity reaction should be evaluated. Some patients were retreated using slower infusion rates at a dose lower than the recommended dose. In patients with severe hypersensitivity, a desensitization procedure to Nexviadyme may be considered. If the decision is made to re-administer the product, extreme caution should be exercised with appropriate resuscitative measures. Once the patient tolerates the infusion, the dose can be increased to the approved dose (see the "*Mode of administration*" section).

In the event of mild to moderate hypersensitivity, the infusion rate may be slowed or temporarily stopped.

Infusion-related reactions

In clinical studies, IRRs have been reported to occur at any time during and/or within a few hours of Nexviadyme infusion and were more likely to occur with higher infusion rates (see the "*Description of certain undesirable effects*" section).

Patients with acute underlying disease at the time of Nexviadyme infusion appear to have an increased risk of IRR. Patients with advanced Pompe's disease may have impaired cardiac and respiratory function, which can predispose them to a higher risk of serious complications from IRRs. Antihistamines, antipyretics and/or corticosteroids can be administered to prevent or reduce IRRs. However, IRRs may still occur in patients who have received pre-treatment.

In the event of a severe IRR, immediate discontinuation of Nexviadyme should be considered and appropriate medical treatment instituted. The benefits and risks of resuming Nexviadyme administration following a severe IRR should be evaluated. Some patients were retreated using slower infusion rates at a dose lower than the recommended dose. Once the patient tolerates the infusion, the dose can be increased to the approved dose (see the "*Mode of administration*" section).

If a mild to moderate IRR occurs independently of pre-treatment, decreasing the infusion rate or temporarily stopping the infusion may improve symptoms (see the "*Description of certain undesirable effects*" section).

Immunogenicity

Treatment-emergent anti-drug antibodies (ADA) have been reported in both treatment-naive (95%) and treatment-experienced (49%) patients.

IRRs and hypersensitivity reactions may occur independently of ADA formation. The majority of IRRs and hypersensitivity reactions were mild to moderate and were managed according to standard clinical practice. In treatment-naïve patients, a trend toward an increased incidence of IRRs was observed with increasing ADA titers, with the highest incidence of IRR (61.5%) reported in the highest ADA titer range (≥ 12,800), compared with an incidence of 24.1% in patients with intermediate ADA titers (1,600 to 6,400), an incidence of 7.1% in those with low ADA titers (100 to 800), and an incidence of 33.3% in those with no ADA.

Due to limited clinical data, the influence of antibody level on clinical efficacy cannot be conclusively assessed. The available data did not show a significant influence of ADA formation on clinical parameters but on pharmacokinetic and pharmacodynamic parameters as a function of titer. Neutralising antibodies (NAb) were detected in some ADA-positive patients (13 patients (21.3%) developed NAb inhibiting both enzyme activity and cell uptake, 4 patients (6.6%) developed NAb inhibiting only enzyme activity, and 10 patients (16.4%) developed NAb inhibiting only cell uptake). The influence of neutralising antibodies on clinical efficacy cannot be conclusively assessed on the basis of the available clinical data either. However, it cannot be excluded that neutralising antibodies have a negative influence on clinical efficacy (see the "*Undesirable effects*" section).
Patients who develop IgE antibodies may be at increased risk of severe infusion-associated reactions with repeated administration of the drug. The development of IgE antibodies to avalglucosidase alfa was detected in one patient.

Testing for ADA may be considered if patients do not respond to treatment. Adverse event-driven immunologic testing, including ADA IgG and IgE, may be considered for patients who are at risk for an allergic reaction or have had a previous anaphylactic reaction to alglucosidase alfa.

Risk of acute cardio-respiratory failure

Caution should be exercised when administering Nexviadyme to patients who may have fluid overload or to patients with underlying acute respiratory disease or impaired cardiac and/or respiratory function for whom fluid restriction is indicated. These patients may be at risk of severe cardiac or respiratory exacerbation during the infusion. Appropriate medical support and monitoring should be readily available during Nexviadyme infusion, and some patients may require extended periods of observation that should be based on their individual needs.

Immune complex-mediated reactions

As with other enzyme replacement therapies, there is a risk of immune complex-mediated reactions such as skin or kidney reactions with Nexviadyme. Although no such cases have been described to date, this risk should be considered in patients treated with Nexviadyme. Urinalysis should be performed regularly in patients with high IgG antibody titers.

Interactions

No studies have been conducted with respect to interactions.

Pregnancy, lactation

Pregnancy

There are no available data on Nexviadyme use in pregnant women. Animal studies do not indicate direct harmful effects with respect to reproductive toxicity. In mice, indirect effects on the foetus were considered to be related to an anaphylactic response to avalglucosidase alfa (see the "*Preclinical data*" section). The potential risk for humans is unknown. Nexviadyme should not be used during pregnancy unless the woman's clinical condition requires treatment with avalglucosidase alfa.

Lactation

There are no available data on the presence of Nexviadyme in human milk, nor on its effect on milk production or on the breast-fed infant. A decision should be made whether to discontinue breast-feeding or to refrain from treatment with Nexviadyme, taking into account the benefit of breast-feeding to the child and the benefit of treatment to the woman.

Fertility

No clinical data are available on the possible effects of Nexviadyme on human fertility. Animal studies in mice have shown no impairment of male or female fertility.

Effects on the ability to drive and use machines

No studies have been performed on the effects of the drug on the ability to drive and use machines. Dizziness has been reported as an IRR and may affect the ability to drive and use machines on the day of infusion.

Undesirable effects

Summary of the safety profile

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

Serious adverse reactions reported in patients treated with Nexviadyme included: headache, dyspnoea, respiratory distress, nausea, discolouration of the skin, chills, chest discomfort, fever, increased blood pressure, increased body temperature, increased heart rate and decreased oxygen saturation. A total of 2 patients receiving Nexviadyme in clinical trials discontinued treatment, including 1 patient due to a serious adverse event. The most frequently reported adverse reactions (> 5%) are headache, nausea, pruritus, rash, urticaria, fatigue and chills. IRRs were reported in 30.4% of patients. The IRRs reported in several patients are as follows: chills, cough, diarrhoea, erythaema, fatigue, headache, flu-like syndrome, nausea, ocular hyperaemia, painful extremities, pruritus, rash, erythaematous rash, tachycardia, urticaria, vomiting, chest discomfort, vertiginous sensation, hyperhidrosis, lip swelling, decreased oxygen saturation, pain, palmar erythaema, tongue swelling, and tremors. The majority of IRRs were rated as mild to moderate.

Adverse reactions (AR) reported in at least 3 patients (≥ 2%) treated with Nexviadyme in the pooled analysis of clinical studies are listed below.

Adverse reactions (reported in at least 3 patients) by organ system class, presented in 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 unknown (cannot be estimated from available data).

Due to the small number of patients, one adverse reaction reported in 3 patients is classified as common. Within each frequency grouping, adverse reactions are presented in the order of decreasing severity.

Infections and infestations

Frequency: Uncommon

- Conjunctivitis*

Immune system disorders

Frequency: Very common

- Hypersensitivity*

Frequency: Common

- Anaphylaxis*

Nervous system disorders

Frequency: Common

Preferred term:

- Headache: 10 patients (7.2%)
- Dizziness: 4 patients (2.9%)

Shakiness*

Frequency: Uncommon

- Paraesthesia*

Eye disorders

Frequency: Common

- Ocular hyperaemia*

Frequency: Uncommon

- Conjunctival hyperaemia*
- Ocular pruritus*
- Increased lacrimal secretion*

Cardiac disorders:

Frequency: Uncommon

- Tachycardia*
- Ventricular extrasystoles*

Vascular disorders:

Frequency: Common

- Hypertension*

Frequency: Uncommon

- Flush*
- Hypotension*

Respiratory, thoracic and mediastinal disorders

Frequency: Common

Preferred term:

- Cough: 3 patients (2.2%)
- Dyspnoea: 3 patients (2.2%)

Frequency: Uncommon

- Tachypnea*
- Laryngeal oedema*
- Respiratory distress*
- Throat irritation*

Gastrointestinal disorders

Frequency: Common

Preferred term:

- Nausea: 8 patients (5.8%)
- Diarrhoea: 3 patients (2.2%)
- Vomiting*
- Lip swelling*
- Tongue swelling*

Frequency: Uncommon

- Abdominal pain*

Skin and subcutaneous tissue disorders

Frequency: Common

Preferred term:

- Pruritus: 13 patients (9.4%)
- Skin rash: 11 patients (8.0%)
- Urticaria: 9 patients (6.5%)
- erythaema: 4 patients (2.9%)
- Palmar erythaema*

Frequency: Uncommon

- Angioedema*
- Hyperhidrosis*

Musculoskeletal and connective tissue disorders

Frequency: Common

Preferred term:

- Muscle spasms: 4 patients (2.9%)
- Myalgia: 4 patients (2.9%)

General disorders and administration site conditions

Frequency: Common

Preferred term:

- Fatigue: 9 patients (6.5%)
- Chills: 7 patients (5.1%)
- Chest discomfort: 3 patients (2.2%)
- Pain: 3 patients (2.2%)
- Flu-like illness*
- Infusion site pain*

Frequency: Uncommon

- Facial pain*
- Hyperthemia*
- Extravasation at the infusion site*
- Joint pain at the infusion site*
- Skin breakout at the infusion site*
- Infusion site reaction*
- Urticaria at the infusion site*
- Localised oedema*
- Peripheral swelling*
- Pyrexia*

Investigation

Frequency: Common

- Increased blood pressure*
- Oxygen desaturation*

Frequency: Uncommon
- Increased body temperature*
- Increased heart rate*
- Breathing seems abnormal*
- Increased complementary factor*
- Increased level of the immune complex*

*These treatment-related adverse events are considered biologically likely to be related to avalglucosidase alfa based on the information on alglucosidase alfa.

In the EFC14028/COMET study, 100 LOPD patients aged 16 to 78 years who had not received enzyme replacement therapy were treated with either 20 mg/kg Nexviadyme (N = 51) or 20 mg/kg alglucosidase alfa (N = 49). 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% of patients treated with alglucosidase alfa in the study discontinued treatment permanently due to adverse events; none of the patients in the Nexviadyme group discontinued treatment permanently. The most frequently reported ADRs (> 5%) were headache, nausea, pruritus, urticaria and fatigue.

Table 1: Most frequently reported ADRs (> 5%) in the EFC14028/COMET study:

Adverse reactions	Nexviadyme (N = 51) N (%)	Alglucosidase Alfa (N = 49) N (%)
Headaches	3 (5.9%)	6 (12.2%)
Nausea	3 (5.9%)	5 (10.2%)
Pruritus	4 (7.8%)	4 (8.2%)
Urticaria	3 (5.9%)	1 (2.0%)
Fatigue	3 (5.9%)	3 (6.1%)

IRRs were reported in 25.5% of patients treated with Nexviadyme compared to 32.7% of those treated with alpha alglucosidase. All IRRs reported in several patients were mild to moderate. No serious IRRs have been reported in patients treated with Nexviadyme.

Description of certain undesirable effects

Hypersensitivity (anaphylaxis included)
In clinical studies, 60 patients (43.5%) experienced hypersensitivity reactions, including 6 patients who reported severe hypersensitivity reactions and 2 patients who experienced anaphylaxis. Some of the hypersensitivity reactions were IgE-mediated. Symptoms of anaphylaxis included respiratory distress, chest pressure, generalised flushing, cough, dizziness, nausea, redness of the palms, swollen lower lip, decreased breathing sounds, redness of the feet, swollen tongue, itching of the palms and feet, and oxygen desaturation. Symptoms of severe hypersensitivity reactions included respiratory failure, respiratory distress and skin rash.

Infusion-related reactions (IRR)
In a pooled analysis of safety data, IRRs were reported in approximately 42/138 (30.4%) of patients treated with Nexviadyme in clinical studies. In clinical studies, 3 of 138 patients (2.2%) reported severe IRRs, including symptoms of chest discomfort, nausea, and increased blood pressure. IRRs reported in more than one patient included symptoms such as chills, cough, diarrhoea, erythaema,

fatigue, headache, flu-like syndrome, nausea, ocular hyperaemia, painful extremities, pruritus, rash, erythaematous rash, tachycardia, urticaria, vomiting, chest discomfort, dizziness, hyperhidrosis, lip swelling, decreased oxygen saturation, pain, palmar erythaema, tongue swelling, and tremors. The majority of IRRs occurred during or within the first 24 hours after administration of Nexviadyme.

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation depends largely on the sensitivity and specificity of the test. In addition, the incidence of positive results observed in an antibody test (including neutralising antibodies) can be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications and underlying pathology. Therefore, comparison of the incidence of antibodies to Nexviadyme in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

The incidence of ADA response to avalglucosidase alfa in patients with Pompe's disease treated with Nexviadyme is shown in Table 2. The median time to seroconversion was 8.3 weeks.

In treatment-naïve adult patients, the occurrence of IRR was observed in both ADA-positive and ADA-negative patients. An increased incidence of IRRs and hypersensitivity was observed with higher ADA IgG titers. For adult patients with prior enzyme replacement therapy (ERT), the incidence of IRRs and hypersensitivity reactions was higher in patients in whom ADAs developed during therapy than in those who did not develop ADAs. One (1) treatment-naive patient and one (1) previously-treated patient experienced anaphylaxis.

In the EFC14028/COMET clinical study, 2 patients reported High Sustained Antibody Titers (HSAT) against Nexviadyme but this was not associated with a loss of efficacy. Cross-reactivity studies of ADAs have shown that the majority of patients produce antibodies that cross-react with alpha alglucosidase. At week 49, specific antibodies to Nexviadyme were detected in 3 patients (5.9%). The ADAs did not affect efficacy parameters, while limited impacts on pharmacokinetics and pharmacodynamics were observed primarily in patients with high antibody titers.

Table 2 - Incidence of treatment-emergent ADAs in patients with Pompe's disease

	Nexviadyme	
	ADA against avalglucosidase alfa in treatment-naive patients[f] (N = 61)	Previously-treated patients ADA against avalglucosidase alfa (N = 55)[e]

	Adults 20 mg/kg every other week (N = 61) N (%)	Adults 20 mg/kg every other week (N = 55) N (%)
ADA at baseline	2 (3.3)	40 (72.7)
Treatment-emergent ADA [a]	58 (95.1)	27 (49.1)
Treatment-induced ADA	56 (94.9)	9 (60.0) [c]
ADA enhanced by the treatment	2 (100) [b]	18 (45.0) [b]
Neutralising antibodies		
The two types of NAb	13 (21.1)	2 (3.6)
Inhibition of enzymatic activity, only	4 (6.6)	8 (14.5)
Inhibition of enzyme absorption, only	10 (16.4)	8 (14.5)

[a] Developed during treatment = treatment induced + treatment enhanced
[b] The incidence of treatment-enhanced ADA is defined as 100 x (patients positive for treatment-enhanced ADA)/(number of evaluable patients with ADA at inclusion).
[c] The incidence of treatment-induced ADA is defined as 100 x (patients positive for treatment-induced ADA)/(number of evaluable patients without ADA at inclusion).
[d] Unknown
[e] Patients previously treated with alglucosidase alfa received this treatment for 0.9-9.9 years before receiving Nexviadyme.
[f] *Includes one paediatric patient*

Paediatric population

Adverse reactions reported in clinical trials in the paediatric population were similar to those reported in adults.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are required to report any suspected new or severe side-effect using the ElViS (Electronic Vigilance System) online portal. You will find information in this respect on: www.swissmedic.ch.

Overdose

Signs and symptoms

No cases of overdose have been reported with Nexviadyme.

Properties/Effects

ATC code

A16AB22

Mechanism of action

Pompe's disease (also known as glycogen storage disease type II, acid maltase deficiency, or Glycogenosis type II) is a rare inherited metabolic muscle disease transmitted in an autosomal recessive manner defined by a deficiency of α-acid glucosidase (AAG), which is required for lysosomal glycogen breakdown. AAG cleaves the alpha-1.4 and alpha-1.6 bonds of glycogen in the acidic environment of the lysosome. Pompe's disease causes intra-lysosomal accumulation of glycogen in various tissues, particularly cardiac and skeletal muscle, leading to the development of cardiomyopathy, progressive muscle weakness and impaired respiratory function.
Avalglucosidase alfa is a recombinant human acidic α-glucosidase (rhAAG) that provides an exogenous source of AAG. Avalglucosidase alfa is a modification of avalglucosidase alfa in which approximately 7 hexamannose structures each containing 2 terminal mannose-6-phosphate (bis-M6P) fragments are conjugated to oxidized sialic acid residues on alpha alglucosidase. Avalglucosidase alfa increases the number of mannose-6-phosphate (M6P) fragments 15-fold compared to alpha alglucosidase. Increasing bis-m6P levels on recombinant human acid alpha-glucosidase increases uptake in the diaphragm and other skeletal muscle via the cation-independent M6P receptor, where it can degrade glycogen and enhance tissue damage. Binding to M6P receptors on the cell surface occurred via carbohydrate groups on the acid alpha-glucosidase molecule, after which it is internalised and transported to lysosomes, where it undergoes proteolytic cleavage resulting in increased enzymatic activity to degrade glycogen.

Pharmacodynamics

In treatment-naive late-onset Pompe's disease patients aged 16 to 78 years, the mean percent change (standard deviation) in urinary hexose tetrasaccharide levels from baseline for patients receiving 20 mg/kg of Nexviadyme every other week and 20 mg/kg of alpha alglucosidase every other week was -53.90% (24.03) and -10.76% (32.33), respectively, at week 49.

Clinical efficacy

The safety and efficacy of Nexviadyme were analysed in clinical studies on treatment-naive and treatment-experienced patients at the time of initiation of treatment.

Clinical trials in patients with late-onset Pompe's disease

Study 1, EFC14028/COMET, was a multinational, multicenter, randomised, double-blind study comparing the efficacy and safety of Nexviadyme and alpha alglucosidase in 100 treatment-naive late-onset Pompe's disease patients 3 years of age and older at the time of initiation of treatment. Patients were randomised in a 1:1 ratio based on baseline forced vital capacity (FVC) value, sex, age, and country to receive 20 mg/kg of Nexviadyme or alpha alglucosidase once every two weeks for 12 months (49 weeks). The study included a long-term, open-label follow-up phase of up to 5 years for all patients, in which patients in the alpha alglucosidase group were switched to treatment with Nexviadyme.

The primary endpoint of study 1 was the change in standing FVC (% of theoretical value) at 12 months from baseline (week 49). At week 49, the change in least squares mean (standard error) for FVC in patients treated with Nexviadyme and alpha alglucosidase was 2.89% (0.88) and 0.46% (0.93), respectively. The clinically significant least squares mean difference of 2.43% (95% CI: -0.13, 4.99) between Nexviadyme and alpha alglucosidase was greater than the predefined non-inferiority margin of -1.1 and achieved statistical non-inferiority (p = 0.0074). The study showed no statistical significance for superiority (p = 0.0626) and the secondary endpoint test was performed without adjustment for multiplicity.

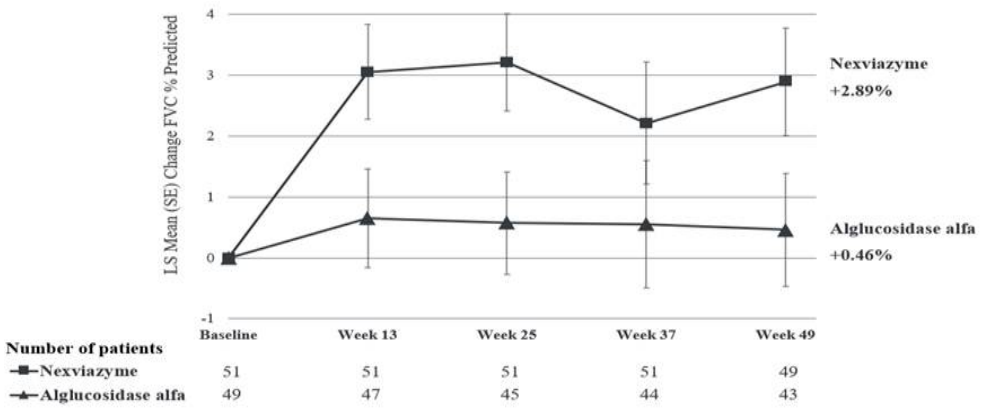
The results for the primary endpoint are presented in Table 3 and Figure 1.

Table 3 - FVC change in least squares mean (% of theoretical value) from baseline to week 49 in standing position

		Nexviadyme (N = 51)	**alpha alglucosidase (N = 49)**
Initial value before starting treatment	Average (standard deviation)	62.5 (14.4)	61.6 (12.4)
Week 49	Average (standard deviation)	65.49 (17.42)	61.16 (13.49)
Estimated change from baseline to week 49 (MMRM)	Least squares mean (standard error)	2.89* (0.88)	0.46* (0.93)
Estimated difference between groups in the change from baseline to week 49 (MMRM)	Least squares mean (95% CI) p-value** p-value***	2.43* (-0.13, 4.99) 0.0074 0.0626	

MMRM: mixed model with repeated measures.
*Based on MMRM, the model includes initial FVC (% of theoretical value, as a continuous effect), sex, age (in years at initial visit), treatment group, visit, interaction between the treatment group and visit as fixed effects.
**Non-inferiority margin of -1.1%
***Superiority not reached

Figure 1: Graph of mean (SE) change in LS versus FVC inclusion (% predicted) in upright position over time in treatment-naive LOPD patients (Study 1)*



The primary secondary endpoint in Study 1 was the change in distance covered in the 6-minute walk test (6MWT) at 12 months from baseline (week 49). At week 49, the least squares mean (standard error) change from baseline for 6MWT in patients treated with Nexviadyme and alpha alglucosidase was 32.21 metres (9.93) and 2.19 metres (10.40), respectively. The clinically significant difference of 30.01 metres in the least squares mean showed a numerical improvement with Nexviadyme compared to alpha alglucosidase. The results for the 6MWT, as well as the other secondary endpoints, are presented in detail in Table 4.

Table 4 - Change in least squares mean from baseline to week 49 for the other secondary assessment criteria

Endpoint	Nexviadyme Change in least squares mean (standard error)	alpha alglucosidase Change in least squares mean (standard error)	Least squares mean difference (95% CI)
Distance covered in metres (6-minute walk test (6MWT)) [a,b]	32.21 (9.93)	2.19 (10.40)	30.01 (1.33, 58.69)
Maximum inspiratory pressure (MIP) (% of theoretical value) [c]	8.70 (2.09)	4.29 (2.19)	4.40 (-1.63, 10.44)
Maximum expiratory pressure (MEP) (% of theoretical value) [c]	10.89 (2.84)	8.38 (2.96)	2.51 (-5.70, 10.73)
Synthetic portable dynamometer scores (HHD)	260.69 (46.07)	153.72 (48.54)	106.97 (-26.56, 240.5)
Total motor function measure score (TMFS)	3.98 (0.63)	1.89 (0.69)	2.08 (0.22, 3.95)
Quality of life health survey (SF-12)	PCS score[d]: 2.37 (0.99) MCS score[e]: 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,d] The MMRM model for 6MWT distance adjusts for % of predicted FVC at baseline and 6MWT (distance covered in metres) at baseline, age (in years, at baseline), sex, treatment group, visit and treatment-visit interaction as fixed effects.
[b] The change in mean from baseline to 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 supraphysiological baseline values of MIP and MEP.
[d] Summary of the physical component.
[e] Summary of the mental component.

In the EFC14028/COMET study, efficacy data were available for 24 patients at week 97, 17 patients at week 121 and 11 patients at week 145. In addition, 9 patients randomised to the alpha alglucosidase group who switched to avalglucosidase alfa after week 49 continued treatment for 2 years. FVC values (in % of theoretical value) remained elevated from baseline until week 97 in 24 patients receiving avalglucosidase alfa who had reached this stage of the study. Efficacy data from the EFC14028/COMET study at week 97 for patients who switched from alpha alglucosidase to avalglucosidase alfa at week 49 showed a numerical improvement in FVC (as % of theoretical value) and 6MWT. In the same study, the mean distance to 6MWT remained elevated from baseline after administration of avalglucosidase alfa until week 145 in 10 patients who had reached this stage.

In an uncontrolled open-label study in patients with late-onset Pompe's disease, FVC (% of theoretical value) and 6MWT showed a consistent effect during long-term treatment with avalglucosidase alfa 20 mg/kg administered once every fortnight for up to 6 years.

Pompe registry
Health professionals or doctors are invited to register their patients with Pompe's disease on the website www.registrynxt.com. Patient data will be collected anonymously in this registry. The objectives of the Pompe registry are to improve knowledge of Pompe's 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.

Pharmacokinetics

The pharmacokinetics of avalglucosidase alfa were evaluated in a population analysis of 75 LOPD patients aged 16-78 years who received between 5 and 20 mg/kg of avalglucosidase alfa every fortnight for up to 5 years.

Absorption

In LOPD patients, for a 4-hour intravenous infusion of 20 mg/kg every fortnight, the mean Cmax and AUC2W were 273 µg/mL (24%) and 1,220 µg.h/mL (29%), respectively.

Distribution

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

Metabolism

Not applicable.

Elimination

In patients with LOPD, the linear clearance predicted by the pharmacokinetic model in the typical population was 0.87 L/h. After a dose of 20 mg/kg every fortnight, the mean plasma elimination half-life was 1.55 hours.

Linearity/non-linearity

Exposure to avalglucosidase alfa increased in a dose-dependent manner between 5 and 20 mg/kg in patients with LOPD. No accumulation was observed after dosing every fortnight.

Immunogenicity

In Study 1, EFC14028/COMET, 96.1% (49 of 51 patients) receiving Nexviadyme developed treatment-emergent anti-drug antibodies. As only 2 patients did not develop anti-drug antibodies, the impact on pharmacokinetics was assessed by classifying patients who developed anti-drug antibodies into 3 peak titre groups: ≤ 800, 1,600-6,400 and ≥ 12,800. Five patients had greater than or equal to 50% change in the area under the curve (AUC) at week 49 from inclusion, but with no clear trend in titres. Inter-subject comparison of the area under the curve (AUC) at days 1 and 2 and week 49 was consistent with the overall analysis of the percentage change in AUC and drug antibody positivity categorised by drug antibody titres. In vitro evaluation of neutralising antibodies that inhibited enzyme activity or cell uptake showed no clear relationship of assay positivity to AUC.

Kinetics in specific patient groups

Population pharmacokinetic analyses in patients with late-onset Pompe's disease showed that age and sex did not significantly affect the pharmacokinetics of alpha avalglucosidase.

Liver failure

The pharmacokinetics of avalglucosidase alfa have not been studied in patients with liver failure.

Impairment of renal function

No clinical studies have been conducted to evaluate the effect of impaired renal function on the pharmacokinetics of alpha avalglucosidase. Based on a population pharmacokinetic analysis of data from 75 patients with late-onset Pompe's disease receiving 20 mg/kg, including 6 patients with mild renal impairment (glomerular filtration rate: 60-89 mL/min; at baseline), no effect of impaired renal function on avalglucosidase alfa exposure was observed.

Preclinical data

Non-clinical data indicate no particular risk to humans based on conventional pharmacological safety, cumulative toxicity and reproductive and developmental toxicity studies. Diphenhydramine (DPH) pre-treatment was administered in almost all studies in mice to prevent or limit a hypersensitivity reaction. DPH was not required for other species.

No carcinogenicity or genotoxicity studies have been conducted with avalglucosidase alfa.

Cumulative toxicity

Repeated doses of avalglucosidase alfa in mice produced quantifiable anti-drug antibody titres and signs consistent with hypersensitivity. The chronic toxicity of avalglucosidase alfa was therefore only assessed in monkeys for 26 weeks. The no observed adverse effect level (NOAEL) in monkeys was the highest dose administered (200 mg/kg avalglucosidase alfa every other week by intravenous route).
The exposure ratio (area under the curve [AUC] exposure to NOAEL at 200 mg/kg qow in monkeys/exposure at 20 mg/kg qow in adult LOPD patients) is 23-fold.

Reproductive toxicity

Avalglucosidase alfa produced no adverse reactions in a combined male and female fertility study in mice at doses up to 50 mg/kg by intravenous route every other day.

In a mouse embryo-foetal toxicity study, administration of avalglucosidase alfa on gestation days 6-15 produced maternal toxicity related to the immunological response (including anaphylaxis) at the maximum dose of 50 mg/kg/day (17 times the steady-state human AUC at the recommended dose of 20 mg/kg every other week for patients with LOPD). This dose also induced a higher post-implantation loss and an average number of late resorptions. Avalglucosidase alfa does not cross the placenta in mice, indicating that the effects on the embryo/foetus were related to maternal toxicity from the immunological response. No malformations or developmental alterations were observed. The developmental NOAEL in mice was 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.
No adverse effects were observed in the embryo-foetal toxicity study in rabbits given avalglucosidase alfa on gestation days 6-19 at doses up to 100 mg/kg/day by IV (91 times the steady-state human AUC at the recommended dose of 20 mg/kg every fortnight for patients with LOPD).

No adverse reactions were observed in a pre- and post-natal developmental toxicity study in mice after administration of avalglucosidase alfa every other day from day 6 of gestation to day 20 postpartum. The NOAEL for maternal reproduction and offspring viability and growth was 50 mg/kg/dose administered by intravenous route.

Toxicity tests in juvenile animals

In juvenile mice, administration of avalglucosidase alfa (up to 100 mg/kg every fortnight by IV) from postnatal day (PND) 21 to PND 77 or 91 had no effect on growth and development. Mortality and clinical signs associated with the immunological response occurred at all dose levels.
The exposure ratio (AUC) of animals at the 100 mg/kg qow dose was 2.1 to 3.7 times greater than the exposure at the 40 mg/kg qow dose used in patients with infantile-onset Pompe's disease (IOPD). As treatment was started at PND 21, the study does not assess the risk for patients under 2 years of age.

Other information

Incompatibilities

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

Shelf life

This medicine should not be used after the expiry date ("EXP") indicated on the container.

Special precautions for storage

Store in the refrigerator (between 2 °C and 8 °C). Avalglucosidase alfa should not be used after the expiry date on the vial.
The reconstituted and diluted solution should be administered without delay. The reconstituted product can be stored for up to 24 hours in the refrigerator at 2 °C to 8 °C and the diluted product can be stored for up to 24 hours in the refrigerator at 2 °C to 8 °C and for up to 9 hours (including infusion time) at room temperature (up to 27 °C).

Instructions for handling

Vials are for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local regulations.

Use aseptic technique during preparation.

1. Determine the number of vials to be reconstituted based on the patient's weight and the recommended dose of 20 mg/kg.
   Patient weight (kg) x dose (mg/kg) = patient dose (mg). Patient dose (in mg) divided by 100 mg/vial = number of vials to be reconstituted. 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, 4 vials should therefore be reconstituted.
2. Remove the number of vials required 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 gradually injecting 10 mL of sterile water for injection into each vial. Each vial will yield 100 mg/10 mL (10 mg/mL). Do not allow water for injection to make contact with the powder and avoid foaming. This is done by pouring the water for injection slowly, drop by drop, into the vial and not directly onto the lyophilised powder. Tilt and roll the vial gently. Do not turn, swirl or shake. Wait for the solution to dissolve. Do not allow air to enter the infusion bag while diluting the product.
4. Immediately inspect reconstituted vials for particulate matter and discolouration. Do not use if the solution is discoloured or if particles are observed.
5. The reconstituted solution should be diluted in 5% aqueous dextrose solution to a final concentration of between 0.5 mg/mL and 4 mg/mL. See Table 7 for total recommended infusion volume based on patient weight.
6. Slowly withdraw the volume of reconstituted solution from each vial (calculated according to the patient's weight).
7. Slowly add the reconstituted solution directly to the 5% dextrose solution. Avoid foaming or shaking the infusion bag. Avoid air ingress into the infusion bag.
8. Turn or gently rub the bag to mix the contents. Do not shake.
9. It is recommended that a 0.2 µm low protein binding in-line filter be used to administer Nexviadyme. When the infusion is complete, flush with 5% aqueous dextrose solution in the infusion bag.
10. Do not infuse Nexviadyme with other products in the same intravenous line.

Table 6: Intravenous infusion volumes for the administration of Nexviadyme by patient weight at doses of 20.

Patient weight range (kg)	Total infusion volume for 20 mg/kg (mL)
1.25 to 10	50
10.1 to 20	100
20.1 to 30	150
30.1 to 35	200
35.1 to 50	250
50.1 to 60	300
60.1 to 100	500
100.1 to 120	600
120.1 to 140	700
140.1 to 160	800
160.1 to 180	900
180.1 to 200	1,000

Authorisation number

67871 (Swissmedic)

Boxes

Packs

Nexviadyme 100 mg/vial, powder for concentrate for solution for infusion.

- Box containing 1 x 100 mg/10 mL single-use glass vial [A]
- Box containing 5 single-use glass vials of 100 mg/10 mL [A]
- Box containing 10 single-use glass vials of 100 mg/10 mL [A]

Marketing authorisation holder

Sanofi-aventis (Switzerland) sa, 1214 Vernier/GE

Date of revision of the text

November 2021