- Reporting suspected adverse reactions after authorization of olipudase alfa is important; it allows continued monitoring of the benefit/risk balance of olipudase alfa
- Healthcare professionals are asked to report any suspected adverse reactions **including medication errors and pregnancy** via the website of Direktoratet for medisinske produkter: www.dmp.no/meldeskjema

Sikkerhetsinformasjon ! Etter krav fra Direktoratet for medisinske produkter

Xenpozyme
(olipudase alfa)

Guide for healthcare professionals - Infusions at Home

(Maintenance Dose Only)

This Guide for health care professionals contains important safety information you need to be aware of when preparing and administering treatment with olipudase alfa in a home setting. Please refer to the Summary of product characteristics (SmPC)/Product information for complete information. SmPC and educational material can be found at www.felleskatalogen.no

Treating Physician:

- Name: .....
- Contact (telephone): .....

Hospital/center:

- Name: .....
- Emergency contact (telephone): .....

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VV-PV-0540178 v1.0 Mai 2023

1 – Objectives

- This Guide is designed to support healthcare professionals in managing the following risks associated with the home use of olipudase alfa:
  - Immunogenicity: infusion associated reactions (IARs), systemic hypersensitivity including anaphylaxis, anti-drug antibody (ADA) mediated hypersensitivity
  - Medication errors in home infusion setting

2 – What is acid sphingomyelinase deficiency (ASMD)?

- ASMD is a rare and potentially life-threatening lysosomal storage disease that results from reduced activity of the enzyme acid sphingomyelinase (ASM), caused by pathogenic variants in the sphingomyelin phosphodiesterase 1 (SMPD1) gene. ASMD is historically known as Niemann-Pick Disease (NPD) types A and B
- The phenotype spectrum ranges from the severe infantile neurovisceral form (ASMD type A) to the chronic visceral form (ASMD type B), with an intermediate or chronic neurovisceral phenotypic presentation also being described (ASMD type A/B)
- ASM catalyzes the hydrolysis of sphingomyelin to ceramide and phosphocholine; the enzymatic deficiency causes an accumulation of sphingomyelin (as well as cholesterol and other cell membrane lipids) in hepatocytes and in cells of the monocyte-macrophage lineage
- Organs in which sphingomyelin accumulates include spleen, liver, bone marrow, lungs, lymph nodes, and brain (in more severe phenotypes)

3 – What is Xenpozyme (olipudase alfa)?

- Xenpozyme is indicated as an enzyme replacement therapy for the treatment of non-central nervous system manifestations of ASMD in pediatric and adult patients with type A/B or type B>
- Xenpozyme is recombinant human ASMD and it provides an exogenous source of ASM reducing the amount of sphingomyelin that accumulates in organs of patients with ASMD

4 – How to mitigate the important risks associated with olipudase alfa treatment?

4A. Immunogenicity: IARs, systemic hypersensitivity including anaphylaxis, ADA mediated hypersensitivity

- Olipudase alfa is **contraindicated** in patients with life-threatening hypersensitivity to the active substance or to any of the excipients when tailored desensitization was unsuccessful
- Olipudase alfa administration **at home** should be **supervised by a healthcare professional** who is trained in emergency measures and has access to appropriate medical support to manage severe reactions, such as those related to systemic hypersensitivity (eg, anaphylaxis)

MONITORING: The patient should be monitored for signs and symptoms of IARs, such as headache, urticaria, pyrexia, nausea and vomiting, and other signs or symptoms of hypersensitivity, closely **during infusion and for an appropriate period of time after the infusion, based on clinical judgment**

- **If IARs or SYSTEMIC HYPERSENSITIVITY including ANAPHYLAXIS occur:**
  - **Discontinue the infusion immediately** and initiate appropriate medical treatment
  - Seek the attention of a physician
  - Contact the treating physician
  - Olipudase alfa treatment should **not be continued at home**
  - Subsequent infusion should only occur in a clinical setting where resuscitation measures are available and re-escalation might be considered

4B. Risk of medication errors in home setting

- Prior to treatment administration:
  - Please read both the instructions for use in the SmPC and the preparation/infusion manual included in this guide carefully
  - Ensure the availability of the following:
    - Resuscitative equipment
    - Patient information (prescribed maintenance dose, weight)
    - Prescriber contact information
    - Necessary supplies and environment (ie, clean environment with electricity, water, telephone access, refrigeration)
  - Carefully prepare the medication referencing the Summary of product characteristics (SmPC) and this Guide

Objectives What is ASMD?
What is Xenpozyme (olipudase alfa)?
How to mitigate the important risks associated with olipudase alfa treatment?
What are the requirements for administration of olipudase alfa at home?
How to administer olipudase
How to reconstitute and dilute olipudase alfa?
Which infusion volumes and rates should be used in children and adults?
Reminders for the HCPs in home infusion setting
Calculation template

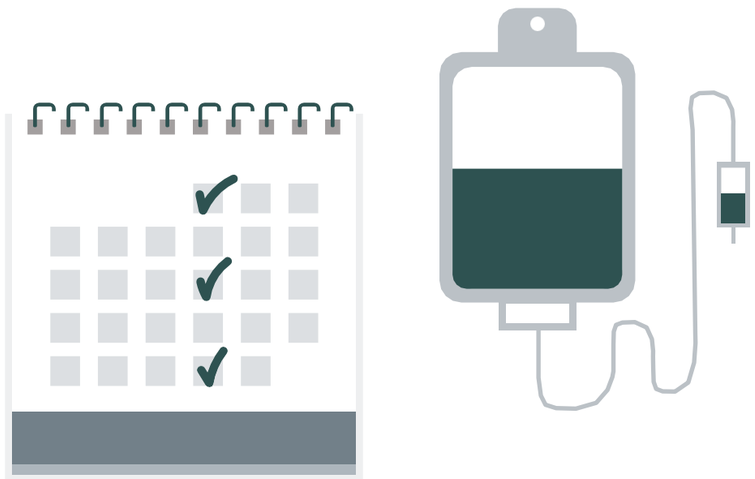
5 – What are the requirements for administration of olipudase alfa at home?

5A. Medical evaluation of the patient before moving to the home infusion setting

- The decision to have patients move to home infusion should be made after evaluation and recommendation by the treating physician
- Only patients on maintenance dose who are tolerating their infusions well can be considered for home infusions
- Olipudase alfa can be administered at home only after successful dose escalation in the clinical setting and in agreement with the treating physician
- The patient and/or caregiver should be informed that home setting should be stopped and subsequent infusion should occur in a clinical setting for re-escalation:
  - If 2 or more consecutive doses are missed
  - If mild, moderate, or severe IARs or systemic hypersensitivity including anaphylaxis occur

5B. Organization of home infusion

- Administration of olipudase alfa should be supervised by a healthcare professional who is trained in emergency measures and has access to appropriate medical support to manage severe reactions and patients/caregivers are aware of that
- Clinical (treatment dose and scheduling) and logistical aspects should be discussed with the patient and/or caregiver by the treating physician before moving to the home setting
- Prior to treatment administration, availability of the following should be ensured:
  - Resuscitative equipment
  - Patient information (ie, prescribed maintenance dose, weight, infusion rate, reconstituted volume, premedication, emergency medication)
  - Prescriber contact information (<available on the patient card>)
  - Necessary supplies and environment (ie, clean environment with electricity, water, telephone access, refrigeration)



5C. Equipment and supplies

- 1 infusion pump, adapted to syringe or infusion bag depending on olipudase alfa dose
- Vials of olipudase alfa (4 mg or 20 mg per vial); must be stored in a clean refrigerator at a temperature of between 2°C and 8°C
- Sterile water for injection to reconstitute olipudase alfa
- NaCl 0.9% solution, 2 x 50 mL, 2 x 100 mL or 2 x 250 mL, depending on olipudase alfa dose, to prepare the final solution for intravenous (IV) administration
- NaCl 0.9% solution, 2 x 50 mL to flush infusion line pre- and post-infusion
- Chlorhexidine 0.5% in alcohol 70% (antiseptic solution)
- Appropriate number of 2 mL, 10 mL and 50 mL syringes depending on number of olipudase alfa vials to be reconstituted. The use of syringes in the preparation of the final solution should also be considered
- 3 sterile hypodermic needles (1.1 x 40 mm)
- 1 infusion needle
- In-line low protein-binding 0.2 µm filter
- Infusion-administration set (infusion line)
- Tape
- Sterile skin cleansing swabs
- Sharps bin
- Hand wash
- Tourniquet
- Additional requisites if using a venous access device: heparin, NaCl 0.9% solution, needles, syringes, dressing pack, sterile gloves, Gripper needle
- Pretreatment medication (if applicable as prescribed)
- Emergency medication (as prescribed)

5D. Pretreatment and emergency treatment

- Appropriate pretreatment and emergency treatment should be provided based on the patient-specific prescription

6 – How to administer olipudase alfa?

- Olipudase alfa is for IV use only
- Olipudase alfa should be administered every 2 weeks. If a dose is missed, please contact the treating physician as subsequent infusions may occur in a clinical setting (see SmPC)
- Prior to administration, please follow instructions on reconstitution and dilution (see **Sections 7 and 8**)
- The infusion solution must be filtered through an in-line low protein-binding 0.2 µm filter during administration
- After the infusion is complete, the infusion line should be flushed with 0.9% NaCl solution for injection using the same infusion rate as the one used for the last part of the infusion

7 – How to reconstitute and dilute olipudase alfa?

7A. Before reconstitution

- Assess patient's clinical condition on the day of infusion
  - If the patient presents with an unresolved adverse effect from the previous infusion or has an acute illness, please contact the treating physician
  - Infusion can be postponed, based on the prescriber's clinical judgment
- Prepare an IV line
- Calculate the patient dose (mg) and determine the number of vials to be reconstituted based on the individual patient's weight and the prescribed dose

Patient dose (mg) = patient weight (kg) x dose (mg/kg)
Number of vials to reconstitute = patient dose (mg) divided by 20 mg/vial

- If the number of vials includes a fraction, round up to the next whole number
- Leave the needed daily number of olipudase alfa vials at room temperature for 20–30 minutes

7B. Reconstitution procedure

- The reconstitution steps must be completed under aseptic conditions. Do NOT use any filters during the reconstitution
- **IMPORTANT: Prevent formation of foam – it will reduce the amount of active enzyme!**

1. In the olipudase alfa vial, inject slowly, against the wall, 5.1 ml of sterile water for preparation of injectables

2. Mix gently by rotating the vial between the palms

3. The resulting solution should be transparent, colorless, and clear. Any vials exhibiting opaque particles or discoloration should not be used

4. The resulting solution contains 4 mg of olipudase alfa per 1 ml

- From a microbiological point of view, the reconstituted solution 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 should normally not be longer than 24 hours at temperatures between 2°C to 8°C, or 12 hours at room temperature (up to 25°C)

7C. Preparation of the infusion solution (calculation)

- Calculate the volume of reconstituted olipudase alfa needed for the infusion, using the following formula:

Volume (ml) = patient dose (mg) ÷ 4 (mg/ml)

- Example 1: A child with body weight of 10 kg on maintenance dose of 3 mg/kg
  - Dose of olipudase alfa needed per infusion is 10 kg x 3 mg = 30 mg
  - Therefore, volume of reconstituted olipudase alfa needed per infusion is 30 mg ÷ 4 mg/ml = 7.5 ml

- Example 2: An adult with body weight of 65 kg on maintenance dose of 3 mg/kg
  - Dose of olipudase alfa needed per infusion is 65 kg x 3 mg = 195 mg
  - Therefore, volume of reconstituted olipudase alfa needed per infusion is 195 mg ÷ 4 mg/ml = 48.75 ml

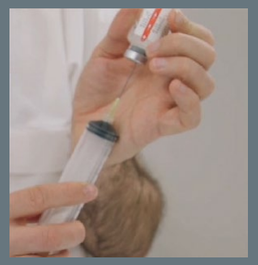
- **Note:** for adults with **body mass index (BMI) ≥30 kg/m²**, the amount of olipudase alfa needed for infusion is determined based on theoretical, not actual, body weight
  - The theoretical body weight is calculated as follows: **30 (kg/m²) x height² (m²)**
  - For example, an individual who is 1,7 m tall and has BMI = 35 kg/m²; has the actual body weight of 101,2 kg (35 kg/m² x 1,7² m²), but their **theoretical body weight** is 86,7 kg (30 kg/m² x 1,7² m²)
  - Dose of olipudase alfa needed per infusion is 86.7 kg x 3 mg = 260 mg
  - Therefore, volume of reconstituted olipudase alfa needed per infusion is 260 mg ÷ 4 mg/ml = 65 ml

7D. Preparation of infusion solution

- The dilution steps must be completed under aseptic conditions. Do NOT use any filters during the dilution
- **Avoid foaming during the dilution steps**
- If **prefilled infusion bags** with 0.9% NaCl solution are used:

1. Determine the total infusion volume (see Section 8) and use the prefilled infusion bag of appropriate size

2. Remove the volume of 0,9% NaCl solution that is equal to the calculated volume of reconstituted olipudase alfa (eg, if 10 ml of reconstituted solution is needed for infusion, first remove and discard 10 ml of NaCl solution)



3. Carefully, collect the calculated amount of 0,9% NaCl solution using a syringe

4. Gently, inject the reconstituted olipudase alfa solution into the infusion bag

- If **empty infusion bags** are used:

1. Determine the total infusion volume (see Section 8) and use the sterile infusion bag of appropriate size

2. Carefully collect the calculated amount of reconstituted olipudase alfa solution using a syringe

3. Gently, inject the reconstituted olipudase alfa solution into the infusion bag

4. Add slowly the sufficient quantity of 0,9% NaCl solution for injection to obtain the required total infusion volume

- **Gently invert infusion bag to mix**. Do not shake. Because this is a protein solution, slight flocculation (described as thin translucent fibres) occurs occasionally after dilution
- From a microbiological point of view, the diluted solution should be used immediately. If not used immediately after dilution, in-use storage times and conditions are the responsibility of the user and should normally not be longer than 24 hours at temperatures between 2°C to 8°C followed by 12 hours (including infusion time) at room temperature (up to 25°C)

8 – Which infusion volumes and infusion rates should be used in children and adults?

CHILDREN

- Determine the total volume of infusion solution and an appropriate delivery container (infusion bag), as described in **Table 1**:
  - Infusion bags: 50, 100, or 250 ml **prefilled with 0,9% NaCl solution** (see **Section 7D**)
    - **Whenever possible, use soft infusion bags to minimize foam formation**
- For children, total perfusion volume for the maintenance dose of **3 mg/kg** can range from **50 to 250 ml**, depending on the child's body weight

Table 1.Volume of the final olipudase alfa solution to deliver the maintenance dose in children (3 mg/kg)

Body weight (kg)	Maintenance dose (mg/kg)	Total perfusion volume (ml)	Delivery container
≥3 and <10	3	50	Infusion bag, 50 ml
≥10 and <20	3	100	Infusion bag, 100 ml
≥20	3	250	Infusion bag, 250 ml

- Follow the instructions for calculation of the volume of reconstituted olipudase alfa needed (see **page 7**) and for preparation of infusion bags for infusion (see **page 8**)
- After preparing infusion solution in the infusion bag, use the following infusion rates to deliver the appropriate maintenance dose (**Table 2**):

Table 2. Olipudase alfa infusion rates: maintenance dose, children (3 mg/kg if no IARs)

Dose (mg/kg)	Infusion steps			Approximate infusion duration (minutes)
	Step	Rate (mg/kg/hour)	Duration (minutes)	
3	1	0,1	20 ± 5	220
	2	0,3	20 ± 5	
	3	0,.6	20 ± 5	
	4	1	160 ± 5	

ADULTS

- For adults, the maintenance doses are delivered using **100 ml infusion bags** only
- Follow the instructions for calculation of the volume of reconstituted olipudase alfa needed (see **page 7**) and for preparation of infusion bags for infusion (see **page 8**)
- Once the 100 ml infusion bags have been prepared, use the infusion rates outlined in **Table 3**

Table 3. Olipudase alfa infusion rates: maintenance dose, adults (3 mg/kg if no IARs)

Dose (mg/kg)	Infusion steps			Approximate infusion duration (minutes)
	Step	Rate (mL/hour)	Duration (minutes)	
3	1	3,.3	20 ± 5	220
	2	10	20 ± 5	
	3	20	20 ± 5	
	4	33,3	160 ± 5	

9 – Reminders for the healthcare professional in home infusion setting

- Olipudase alfa administration should be supervised by an healthcare professional **who is trained in emergency measures and has access to appropriate medical support** to manage severe reactions, such as those related to systemic hypersensitivity (eg, anaphylaxis)
- **Dose and infusion** rate should remain as defined by the treating physician while infusing the patient at home and should not be changed without the supervision of the treating physician
- **Monitor the patient** in case of any signs and symptoms of IARs or systemic hypersensitivity including anaphylaxis and **contact the treating physician.** Subsequent infusion might take place in the clinical setting
- **Contact the treating physician** if infusion is missed (ie, a delay of >3 days). Re-escalation in the clinical setting may be required if 2 or more consecutive doses have been missed
- Check if you have sufficient supplies and request orders as necessary

10 – Calculation template

Patient dose

-	X		=	
Patient weight (kg)		Prescribed dose (mg/kg)		Patient dose (mg)

Number of vials for reconstitution

-	/	20	=	
Patient dose (mg)		Amount of olipudase alfa in a vial (mg)		Number of vials

Please proceed with reconstitution as described in **Section 7B** (*see* **page 6**)

Volume of reconstituted olipudase alfa solution needed for infusion

-	/	4	=	
Patient dose (mg)		Concentration of olipudase alfa in reconstituted solution (mg/ml)		Volume (ml)

Total infusion volume (adults)

100 *For adults receiving maintenance dose 3 mg/kg*

Volume (ml)

Total infusion volume (children)

-

To determine total infusion volume for children please see ***Section 8*** *on* ***page 9*** ***(Table 1)***

Volume (ml)

Please proceed with preparation of the infusion solution as described in **Section 7C** (*see* **page 8**)

Please repeat the calculation if patient's body weight has changed or if prescribed dose has been changed by the treating physician

PLEASE KEEP A RECORD OF ALL CALCULATIONS

Notes

10 – Calculation template

Patient dose

_____ (Patient weight (kg)) **X** _____ (Prescribed dose (mg/kg)) = _____ (Patient dose (mg))

Number of vials for reconstitution

_____ (Patient dose (mg)) / **20** (Amount of olipudase alfa in a vial (mg)) = _____ (Number of vials)

Please proceed with reconstitution as described in **Section 7B** (*see* **page 6**)

Volume of reconstituted olipudase alfa solution needed for infusion

_____ (Patient dose (mg)) / **4** (Concentration of olipudase alfa in reconstituted solution (mg/ml)) = _____ (Volume (ml))

Total infusion volume (adults)

100 (Volume (ml)) *For adults receiving maintenance dose 3 mg/kg*

Total infusion volume (children)

_____ (Volume (ml)) *To determine total infusion volume for children please see* ***Section 8*** *on* ***page 9*** ***(Table 1)***

Please proceed with preparation of the infusion solution as described in **Section 7C** (*see* **page 8**)

Please repeat the calculation if patient's body weight has changed or if prescribed dose has been changed by the treating physician

PLEASE KEEP A RECORD OF ALL CALCULATIONS

Notes