POMBILITI ▼ (CIPAGLUCOSIDASE ALFA) + OPFOLDA (MIGLUSTAT)

INFORMATION PACK FOR HEALTHCARE PROFESSIONALS

Prescriber guide on pregnancy and home infusion

VERSION 1.0

IMPORTANT SAFETY INFORMATION:

Healthcare Professionals involved in the prescribing or administration of Pombiliti (cipaglucosidase alfa) and Opfolda (miglustat) must read and understand the information contained within this pack.

For complete safety information please refer to the Summary of Product Characteristics (SmPC) for cipaglucosidase alfa and miglustat, available on the Great Britain (GB) and Northern Ireland (NI) electronic medicines compendium websites: For cipaglucosidase alfa; **www.medicines.org.uk/emc/product/14898** and for miglustat; **www.medicines.org.uk/emc/product/14904**

▼ 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 using the Yellow Card Scheme via **www.mhra.gov.uk/yellowcard** or by searching for MHRA Yellow Card in the Google Play or Apple App Store.

Adverse reactions should also be reported to Amicus Medical Information on: Tel: **08082346864**; email: **drugsafety@amicusrx.com**

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This guide comprises of two sections:

Part A: Cipaglucosidase alfa + miglustat

PRESCRIBER GUIDE ON PREGNANCY

The potential for pregnancy must be assessed for all female patients prescribed cipaglucosidase alfa in combination with miglustat and patients should be sufficiently counselled about the risks associated with exposure during pregnancy.

A woman has the potential for pregnancy if one of the following applies:

A woman of childbearing potential who:

1) has not had a hysterectomy or bilateral oophorectomy

2) has menstruated at a certain point in the last 24 consecutive months and is not considered to be postmenopausal.

Background of risk

- Animal studies with cipaglucosidase alfa in combination with miglustat have shown reproductive toxicity including certain cardiovascular birth defects, pre-implantation loss, and increased mortality in mothers and/or their offspring.
- There are no clinical data from the use of cipaglucosidase alfa in combination with miglustat in pregnant women.

Patient counselling recommendations

- Cipaglucosidase alfa in combination with miglustat is not to be used in women of childbearing potential who are not using reliable contraception.
- Reliable contraceptive measures must be used by women of childbearing potential during treatment with cipaglucosidase alfa in combination with miglustat, and for 4 weeks after discontinuing treatment.
- Patients should contact their treating physician immediately if they become pregnant.

CIPAGLUCOSIDASE ALFA + MIGLUSTAT RISK MINIMISATION **GUIDE FOR HEALTHCARE PROFESSIONALS**

Prescriber counselling requirements

It is the treating physician's responsibility to counsel fully their female patients of childbearing potential on the risk of exposure while pregnant and the need for reliable contraceptive measures. Full counseling (including all of the points below) should be provided at treatment consultation/initiation and patients should be reminded during follow-up consultations not to become pregnant while receiving treatment.

The following points should be covered:

- Animal studies with cipaglucosidase alfa in combination with miglustat have shown reproductive toxicity including certain cardiovascular birth defects, pre-implantation loss, and increased mortality in mothers and/or their offspring.
- There are no clinical data from the use of cipaglucosidase alfa in combination with miglustat in pregnant women.
- The patient must use reliable contraception during and for 4 weeks after stopping treatment with cipaglucosidase alfa and miglustat.
- The patient must not become pregnant whilst undergoing treatment, and for 4 weeks following cessation of therapy.
- The patient should immediately notify their physician if they become pregnant or wish to conceive a child.
- If the patient wishes to conceive a child, treatment should be stopped, and the patient should not conceive within 4 weeks of stopping treatment.
- Treatment is not recommended during breastfeeding too, so alternative feeding methods should be sought should the patient wish to reinstate their treatment following the birth of their baby.
- Women intending to conceive should be advised on the benefits and risks of stopping treatment.

Part A: Cipaglucosidase alfa + miglustat

PRESCRIBER GUIDE ON PREGNANCY

Please use this patient reminder card to advise all female patients of childbearing potential of the importance to avoid pregnancy while on treatment and for 4 weeks after having stopped treatment.

→ To order further copies of the patient reminder card please email: **info@amicusrx.co.uk** or call: **01753 888 567**

▼ **This medicinal product is subject to additional monitoring.**

This will allow quick identification of new safety information. Health professionals are encouraged to report any suspected case of side effects using the Yellow Card Scheme via **www.mhra.gov.uk/yellowcard** or by searching for MHRA Yellow Card in the Google Play or Apple App Store.

Pregnancies occurring during treatment and within 4 weeks following discontinuation of treatment should be reported to the MHRA and the company listed in the patient's package information leaflet who will follow up with you to record the pregnancy outcome. Healthcare professionals are asked to report any suspected adverse reactions. Adverse events should be reported to the MHRA and Amicus listed in the patient's package information leaflet. Reporting forms and information can be found at **www.mhra.gov.uk/yellowcard** or search for MHRA Yellow Card in the Google Play or Apple App Store. Signature of parent or legal guardian is necessary if the patient is under the age of 18.

Healthcare professionals are asked to report any suspected adverse reactions, pregnancies and consider registering patients in the Amicus Pompe Disease registry (registry contact email: **info@amicusrx.co.uk**).

Patient Reminder Card for Pombiliti▼(cipaglucosidase alfa) + Opfolda (miglustat) for women of childbearing potential

You have been given this card because you have been prescribed cipaglucosidase alfa and miglustat. Please read this card and the package information leaflet thoroughly before starting your treatment with cipaglucosidase alfa and miglustat.

▼ 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 **www.yellowcard.mhra.gov.uk** for how to report side effects. Or search for MHRA Yellow Card in the Google Play or Apple App Store.

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Reminder for women of childbearing potential

- Cipaglucosidase alfa is a type of 'enzyme-replacement therapy' (ERT) that is used in the treatment of late-onset Pompe disease in adults.
- Cipaglucosidase alfa is always used with another medicine called miglustat. It is very important that you read the separate Patient Information Leaflets for both cipaglucosidase alfa and miglustat before starting treatment.
- Cipaglucosidase alfa and miglustat has been prescribed for you only. Do not share this medication with anybody.

Important information to know:

→ **Pregnancy:** Do not take cipaglucosidase alfa in combination with miglustat if you are pregnant. Be sure to tell your doctor immediately if you become pregnant, think you may be pregnant, or are planning to become pregnant. There may be risks to your unborn child.

Breastfeeding: Cipaglucosidase alfa in combination with miglustat should not be used in women whilst breastfeeding. Be sure to discuss your options with your doctor.

Contraception: Women of childbearing potential must not become pregnant and should maintain reliable contraceptive methods during, and for 4 weeks after, treatment with cipaglucosidase alfa in combination with miglustat.

POCKET PLACEMENT

Part B: Cipaglucosidase alfa healthcare professional guide to minimise risk associated with cipaglucosidase alfa home infusions

CONTENTS

1 CONTENT AND OBJECTIVES

Cipaglucosidase alfa infusion therapy, in combination with miglustat, is available for treatment of patients with Pompe disease. To improve convenience and quality of life, the intravenous treatment can be administered in the patient's home if specific requirements can be fulfilled.

About this guide

The purpose of this guide for physicians and healthcare professionals is to minimise the risk for medication errors when cipaglucosidase alfa is administered at home, and to provide clear guidance on the following:

- → **Which patients may be eligible for home infusion, and how to organize home infusions, including premedication and emergency treatment of infusion reactions;**
- → **Preparation, reconstitution, and administration of the product at home;**
- → **Recognition and management of adverse drug reactions, including infusion associated reactions (IARs), and possible actions for the management of adverse drug reactions when symptoms occur.**

The home infusion takes place under the responsibility of the treating physician. Distribution of the manual for patients with Pompe disease who receive home infusion of cipaglucosidase alfa should only be executed if the treating physician decides that the patient is eligible for home infusion treatment.

The processes presented in this document serve as overall guidance but are subject to local medical practice and national rules and regulations.

CIPAGLUCOSIDASE ALFA + MIGLUSTAT RISK MINIMISATION **GUIDE FOR HEALTHCARE PROFESSIONALS**

2 ASSESSING ELIGIBILITY FOR HOME INFUSION

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. Before making any arrangements, the treating physician must determine if the patient fulfils the following primary criteria for a home infusion:

(SEE ALSO THE PRESCRIBING INFORMATION)

- → The patient must be tolerating their infusions well, and have no history of moderate or severe IARs for a few months.
- → The patient must have received cipaglucosidase alfa infusions supervised by a physician with expertise in management of Pompe disease patients for a few months in a hospital or clinic setting. 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 considered medically stable. A comprehensive evaluation must be completed before the initiation of home infusion.
- → The patient must have a history of adherence to the prescribed dosing schedule and miglustat fasting requirements.
- → The patient must be willing and able to comply with home infusion procedures.

3 REQUIREMENTS AND ORGANISATION OF HOME INFUSION

3.1 Patient

GENERAL

- The patient and/or caregiver(s) **have been informed by the treating physician about the treatment to be provided at home, the associated risks with providing treatment at home** (like hypersensitivity reactions, IARs, and medication errors), and must agree to the treatment at home.
- The patient and/or caregiver(s) **have an understanding of the illness and are able to recognize adverse events like hypersensitivity reactions and IARs**, and understand the procedure to be followed should these occur.
- **The home environment must be conducive to home infusion therapy** including a clean environment with electricity, water, telephone access and physical space to support storage of cipaglucosidase alfa and any infusion equipment. The home infusion service provider will provide a temperature controlled fridge, appropriate for the storage of 1-2 doses of cipaglucosidase alfa, and associated infusion supplies.
- The patient and/or caregiver(s) **have an understanding that cipaglucosidase alfa should always be administered in combination with miglustat**, and that miglustat should always be administered 1 hour prior to the cipaglucosidase alfa infusion. In the event of infusion delay, the start of infusion should not exceed 3 hours from taking miglustat. If the cipaglucosidase alfa infusion cannot be started within 3 hours of oral administration of miglustat, reschedule treatment of cipaglucosidase alfa and miglustat at least 24 hours after taking miglustat. If cipaglucosidase alfa and miglustat are both missed, treatment should occur as soon as possible.
- The patient has been **informed that the infusion is administered by a nurse of other healthcare professional**.
- **Patients experiencing adverse events (or the patient's caregiver) must inform the home infusion healthcare professional/nurse or contact the treating physician immediately.** Subsequent infusions may need to occur in a hospital or other medical setting.

MEDICAL

- The patient must be **physically and mentally able** to undergo the infusions at home.
- The patient has **venous access or a central venous access device** that allows adequate infusion.

CIPAGLUCOSIDASE ALFA + MIGLUSTAT RISK MINIMISATION **GUIDE FOR HEALTHCARE PROFESSIONALS**

Patients with acute underlying respiratory illness or compromised cardiac and/or respiratory function

Patients with acute underlying respiratory illness or compromised cardiac and/or respiratory function may be at risk of serious exacerbation of their cardiac or respiratory function during infusions. Appropriate medical support and monitoring measures should be readily available during cipaglucosidase alfa infusion.

Patients at particular risk of infusion-related reactions include:

- Patients with an acute illness at the time of the infusion. This must be discussed with the treating physician before the start of the infusion and additional monitoring of the patient for a longer period may be necessary.
- Patients with advanced Pompe disease and impaired cardiac and respiratory function. Such patients may require resuscitation measures during the infusion. Suitable measures for medical support and monitoring should be carried out in accordance with the information provided by the physician.
- Patients at risk of volume overload (eg compromised cardiac and/or respiratory function). These patients are at risk of infusion-related volume overload to a serious deterioration of their cardiac or respiratory condition up to cardiopulmonary failure. Appropriate measures of medical support and monitoring should be available during the infusion, as determined by the physician, and some patients may need to be monitored for a longer period as determined by the physician.

3.2 Treating physician

- **The home infusion takes place under the responsibility of the treating physician.** Distribution of the manual for patients who receive home infusion of cipaglucosidase alfa to the infusion healthcare professional and patient/caregiver(s) should only be executed if the treating physician decides that the patient is eligible for home infusion treatment. It is the responsibility of the treating physician to **ensure a safe administration to the patient in order to avoid risks of medication errors and IARs including hypersensitivity and anaphylactic reactions.** This should be checked and documented by the treating physician.
- The treating physician **decides whether to delegate** the home administration to an infusion healthcare professional/nurse and, **if delegated, that the administration of the medicinal product and any necessary monitoring of the patient, premedication, and emergency treatment are designed safely.**

If administration of the drug is delegated, it is the treating physician's responsibility to:

- Provide training and information to the healthcare professionals/nurses (or ensure they are appropriately qualified) and to the patients and/or caregivers;
- Determine the correct dosage and infusion rate of cipaglucosidase alfa;
- Create an individual emergency plan with precise instructions and contact options;
- Identify the required infusion materials and suitable premedication and rescue medication;
- Inform healthcare professionals/nurses of the appropriate dosage, infusion rate and actions, and that the individually created emergency plan is not to be changed without explicit instructions from the treating physician.
- Any changes must be clearly communicated to the patient and/or caregiver(s), and to the healthcare professional that is supervising the preparation and administration of cipaglucosidase alfa. It is recommended that the treating physician documents all of these measures and their implementation in the infusion diary.

- The treating physician is responsible for the **initiation of all necessary administrative actions** which allows the other parties involved (patient and/or caregiver(s), infusion healthcare professional/nurse, pharmacy) to proceed.
- The treating physician is **responsible for providing the patient with the "Manual for patients with Pompe disease who receive home infusion of cipaglucosidase alfa," which includes the infusion diary.** The infusion rate of cipaglucosidase alfa that was tolerated by the patient in a more controlled setting (eg in the hospital or other medical setting) must not be changed in the home setting, unless necessary due to safety considerations. Any changes in cipaglucosidase alfa administration must be clearly documented in the infusion diary.
- Pre-infusion treatment, if administered in the hospital or other medical setting (e.g. antihistamines, antipyretics, and/or corticosteroids), must be provided **based on the patient-specific prescription and should be described in the infusion diary.** This treatment must not be altered in the home setting, unless medically warranted at the discretion of the treating physician.
- Emergency treatment must be provided **based on the patient-specific prescription and should be described in the infusion diary.**
- The treating physician must **ensure that a rapid and reliable line of communication is available** to the infusion healthcare professional/nurse should the home-infused patient experience an IAR and medical advice is sought.
- **Regular disease monitoring of the home-infused patient** is the responsibility of the treating physician.

- **Appropriate scheduling and monitoring of the infusions** is the responsibility of the treating physician and infusion healthcare professional/nurse.

- **The treating physician, in coordination with the infusion healthcare professional/nurse, must report all suspected adverse reactions and medication errors to Amicus Therapeutics as described in Section 7.**

3.3 Infusion healthcare professional/nurse

- The infusion healthcare professional/nurse has a **coordinating role** regarding the treating physician and the patient and/or caregiver(s) in organizing the treatment at home, and establishes with the treating physician, patient and/or caregiver(s) the level of support necessary in the home.
- Is in **close contact with the treating physician** in accordance with the agreement made and regularly informs the physician about the progress of the treatment.
- The infusion healthcare professional/nurse is **qualified to give IV infusions, has been appropriately trained on the administration of cipaglucosidase alfa in combination with miglustat, and has been trained on the possible adverse events** (including serious adverse events such as anaphylactoid reactions) **and the actions to be taken** should they occur.
- The infusion healthcare professional/nurse **strictly follows the prescribed method of preparation and administration** of cipaglucosidase alfa in combination with miglustat as stated in this Guide and the prescribing information.
- The infusion healthcare professional/nurse **strictly follows the prescribed dose and infusion rate** of cipaglucosidase alfa as stated in the infusion diary.
- **Appropriate scheduling and monitoring of the infusions** is the responsibility of the treating physician and infusion healthcare professional/nurse.
- The infusion healthcare professional/nurse **records each administration** of cipaglucosidase alfa in the infusion diary.
- The infusion healthcare professional/nurse is **available at all times during the home infusion and for a specified time after infusion**, depending on patient's tolerance prior to starting home infusion.

- **Appropriate management of IARs including reduction of the infusion rate, temporary interruption of the infusion, symptomatic treatment with oral antihistamine, or antipyretics, and appropriate resuscitation measures** is the responsibility of the infusion healthcare professional/nurse. Refer to Section 6 for further guidance.
- The infusion healthcare professional/nurse **documents each infusion, describing the patient's medical condition before and after the infusion, the dosage, the infusion rate, any side effects/emergencies encountered and their treatment.**
- Any **IAR including hypersensitivity and anaphylactic reactions** must be recorded in the infusion diary.
- The infusion healthcare professional/nurse **consults with the treating physician regarding returning the patient to hospital/clinic administration** for subsequent infusions.

- **The infusion healthcare professional/nurse, in coordination with the treating physician, must report all suspected adverse reactions and medication errors to Amicus Therapeutics as described in Section 7.**

3.4 Medical examination of the patient before administering the home infusion

Before the cipaglucosidase alfa infusion is administered, the patient's fitness to be infused should be established. The patient should be in good general condition and well-being according to their individual disease status.

The presence of acute as well as febrile illness should be excluded. The patient should be questioned as to whether any adverse reactions occurred in association with the previous infusion (ie, after the infusion healthcare professional/nurse left the patient's home). Blood pressure, pulse, respiration rate and body temperature should be checked regularly at the beginning and also during the infusion, particularly before any increase in the infusion rate.

In case of intercurrent illness or newly reported adverse reactions in association with previous infusion, consultation is required with the treating physician before starting the infusion.

3.5 Pre-treatment and emergency treatment

- **Premedication with oral antihistamine, antipyretics, and/or corticosteroids may be administered to assist with signs and symptoms related to IARs. Appropriate pre-treatment should be provided based on the patient-specific prescription.** Treatment administered in the hospital or other medical setting should not be altered in the home setting unless medically warranted at the discretion of the treating physician.
- **Medications must be available to respond to an emergency situation**, if necessary. Proper education on the use of emergency medications must be provided by the treating physician to the home infusion healthcare professional/nurse.
- **In the event the patient experiences an IAR, appropriate management including reduction of the infusion rate, temporary interruption of the infusion, symptomatic treatment with oral antihistamine, or antipyretics, and appropriate resuscitation measures should be considered.** Section 6 provides a guideline for management of IARs; however, the list of IAR symptoms is not comprehensive and is meant to serve as a guideline to the infusion healthcare professionals/nurses for the initial management of IARs, including anaphylaxis. It is at the treating physician's discretion to follow the guidelines or implement the treatment protocol that their centre is accustomed to following.
- **In the event the patient experiences anaphylaxis or a severe allergic reaction** during or shortly after the infusion, **the infusion should be immediately stopped and appropriate medical treatment should be initiated.** If the patient continues therapy, their next infusions **must occur in a hospital** or other medical setting equipped to deal with such medical emergencies.

3.6 The infusion diary

- The infusion diary serves as a **means of communication for all involved** in administering cipaglucosidase alfa in combination with miglustat in the home-setting.
- The infusion healthcare professional/nurse **records the findings and actions** from the initial infusion and all relevant information from subsequent infusions in the infusion diary.
- **An emergency contact list must be completed** and available at home in the infusion diary for the patient and/or caregiver(s) and the infusion healthcare professional/nurse.
- The infusion diary must be **kept at the patient's home** and is updated by the infusion healthcare professional/nurse and/or patient/caregiver(s) each time cipaglucosidase alfa is administered.

- The patient/caregiver **must take the infusion diary to the hospital/clinic** at each appointment and bring it home afterwards.
- In the infusion diary, **the treating physician clearly states the dose, the required reconstituted volume, infusion rate, as well as any changes.**
- The treating physician clearly states what has to be done, which **pre-medications should be administered,** and **which medications are to be administered in the event of a serious IAR** in line with current medical standards for emergency treatment.
- The **contact details of the treating physician** and the country-specific national emergency number are documented in the infusion diary.

4 HOME INFUSION PROCEDURE

The treating physician is responsible for the organization of the home infusion and needs to agree upon the home infusion procedure and ensure the home infusion healthcare professional/nurse is appropriately qualified.

The infusion healthcare professional/nurse carries out the entire procedure for the infusions at the patient's home. The infusion healthcare professional/nurse is available at all times during the home infusion and for a specified time after infusion, depending on patient's tolerance prior to starting home infusion.

The preparation/administration procedures described in **Section 5** of this document must be adhered to, and each administration of cipaglucosidase alfa should be recorded in the infusion diary (**Section 3.6**). In case of any problems with the reconstitution and administration of cipaglucosidase alfa, the infusion healthcare professional/nurse should consult with the treating physician to determine appropriate action before restarting or continuing the infusion.

The healthcare professional/nurse should ensure they provide the patient with the cipaglucosidase alfa patient information leaflet at the time of infusion. Patients should be advised to consult the information leaflet concerning potential adverse events and inform their home infusion healthcare professional/nurse, or treating physician directly, if they have any concerns about adverse events or receiving the treatment at home.

5 PREPARATION AND ADMINISTRATION OF CIPAGLUCOSIDASE ALFA

Instructions for use relating to the reconstitution, dilution and administration can be found in sections 5.4 to 5.8 below and in the Summary of Product Characteristics (SmPC). The SmPC is available online at www.medicines.org.uk/emc/product/14898

5.1 Prescription

The miglustat dose, cipaglucosidase alfa dose, required reconstituted volume, infusion rate, premedication, emergency medication, as well as any changes is determined by the treating physician and documented in the infusion diary. Any changes to this prescription must be recorded in the infusion diary.

Because cipaglucosidase alfa is administered in a weight-adjusted dose, it is important to check the patient's weight regularly to ensure correct dosing. In the case of delegation, the treating physician must determine how to deal with the dosage in the event of a change in weight. To avoid medication errors, the correct determination of the required infusion volume is of great importance and should be determined in advance by the treating physician.

5.2 Supplies

TREATMENT DAY CHECKLIST

PRODUCTS

- ☐ **Cipaglucosidase alfa 105 mg vials** (20 mg/kg body weight administered every other week)
- ☐ **Miglustat capsules** (for patients ≥50 kg, 4 capsules [260 mg total]; for ≥40 kg to <50 kg, 3 capsules [195 mg total])
- ☐ Premedications as prescribed

INFUSION SUPPLIES & EQUIPMENT

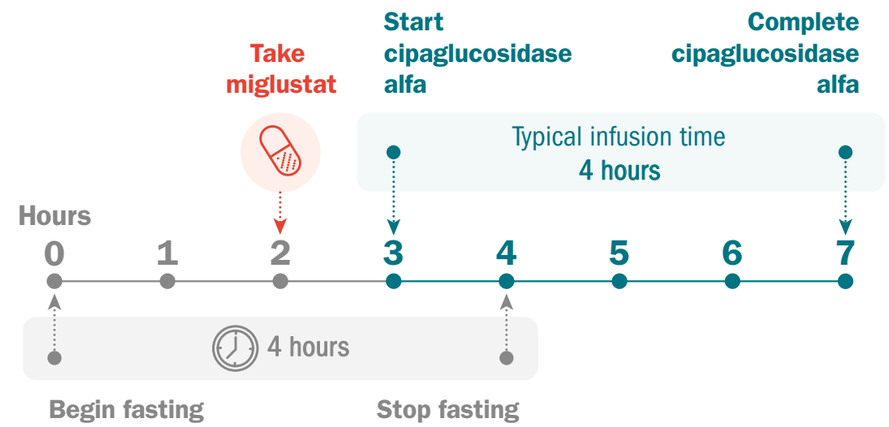
- ☐ **Sterile water** for injection at room temperature of 20°C to 25°C
- ☐ **Sodium chloride 9 mg/mL (0.9%) solution** for injection at room temperature of 20°C to 25°C – Choose a bag size based on the patient's body weight
- ☐ **A needle that has a diameter of 18 gauge or less** – Do not use filter needles that reduce particulate during preparation
- ☐ **Additional supplies** per institution protocol

CIPAGLUCOSIDASE ALFA + MIGLUSTAT RISK MINIMISATION **GUIDE FOR HEALTHCARE PROFESSIONALS**

5.3 Timeline to administration including administration of miglustat

Cipaglucosidase alfa is only to be administered in conjunction with miglustat. The use of miglustat with any other GAA enzyme replacement therapy has not been studied.

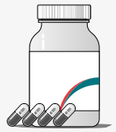
What the infusion day should look like:



If the patient is switching from another enzyme replacement therapy (ERT), treatment with cipaglucosidase alfa + miglustat can be started at the next scheduled dosing time—2 weeks after the previous treatment. Patients who have switched from another ERT to cipaglucosidase alfa + miglustat therapy should be advised to continue with any premedications used with the previous therapy to minimize infusion-associated reactions (IARs).

DOUBLE-CHECK THE FOLLOWING

- The patient has been fasting for 2 hours before and 2 hours after taking miglustat
- They've taken the miglustat capsules approximately 1 hour before the infusion is due to begin and it has not been more than 3 hours since they've taken miglustat prior to infusion initiation



TAKING MIGLUSTAT

- Capsules should be taken on an empty stomach
- The patient must **fast 2 hours before and 2 hours after taking miglustat**
- Capsules should be taken approximately **1 hour before the start of cipaglucosidase alfa infusion**
    - In the event of infusion delay, the start of infusion should not exceed 3 hours from the oral administration of miglustat
- Capsules should be swallowed with water, fat-free (skimmed) cow's milk, and tea or coffee with no cream, sugars, or sweeteners. These beverages can be consumed during this 4-hour fasting period
- Two hours after taking miglustat, the patient can resume normal eating and drinking

CIPAGLUCOSIDASE ALFA + MIGLUSTAT RISK MINIMISATION **GUIDE FOR HEALTHCARE PROFESSIONALS**

5.4 Dosing for both cipaglucosidase alfa + miglustat is based on body weight

If the patient's weight has changed since their last infusion, or if you haven't administered cipaglucosidase alfa + miglustat to the patient before, you will need to weigh the patient. In the case of delegation, the treating physician must determine how to deal with the dosage in the event of a change in weight. To avoid medication errors, the correct determination of the required infusion volume is of great importance and should be determined in advance by the treating physician. Please consult treating physician to confirm the correct dose before initiating infusion.

Calculating the dose

Cipaglucosidase alfa is administered to the patient by intravenous infusion every other week in conjunction with the oral medication miglustat.

Weight-based dosing

Recommended dosage: 20 mg/kg total body weight administered every other week as an intravenous solution

Miglustat capsules of 65 mg are administered every other week in conjunction with the intravenous infusion cipaglucosidase alfa.

Weight-based dosing

Recommended dosage:
- ≥ 40 kg but < 50 kg = 3 capsules
- ≥ 50 kg = 4 capsules

	Calculation	Example	
Dose	Patient's body weight (kg) x dose (20 mg/kg)	65 kg x 20 mg/kg = 1300 mg total dose	
Vials to reconstitute	Patient's dose (in mg) divided by 105 (mg/vial)	1300/105 mg per vial = **12.38 vials**	
Vials to prepare	Round up to the nearest whole vial	12.38 vials → 13 vials	
Calculate extraction volume	Number of full vials x 7.0 mL/ bottle extraction volume	**12** vials x 7.0 mL = **84 mL**	**0.38** vial x 7.0 mL = **2.7 mL**
		84 mL + 2.7 mL = **86.7 mL extraction volume**	

5.5 Preparing for reconstitution

Before cipaglucosidase alfa can be administered to the patient, it must be reconstituted. Once you know how many vials you'll be using, take them out of the refrigerator and let them stand for about half an hour to reach room temperature of 20°C to 25°C.

ITEMS NEEDED FOR RECONSTITUTION AND DILUTION

Cipaglucosidase alfa 105 mg vials

Sterile water for injection at room temperature of 20°C to 25°C

Sodium chloride 9 mg/mL (0.9%) solution for injection at room temperature of 20°C to 25°C

- Choose a bag size based on the patient's body weight

A needle that has a diameter of 18 gauge or less

- Do not use filter needles that reduce particulates during preparation

INSPECT EACH VIAL CAREFULLY

Clear to opalescent, colourless to slightly yellow, and appears almost free of particles, but may contain white-to-translucent particles.

Do not use if foreign matter is observed or discoloured or if the closure is damaged or the button of overseal is removed.

5.6 Reconstituting the lyophilised cake/powder

1

Remove vials from the refrigerator (2°C to 8°C) and allow to come to room temperature (ie, approximately 30 minutes at 20°C to 25°C).

2

Reconstitute each vial by slowly adding 7.2 mL sterile water for injection dropwise down the inside of the vial rather than directly onto the lyophilised cake or powder. Avoid forceful impact of sterile water for injection on the lyophilised powder and avoid foaming.

3

Tilt and roll each vial gently to dissolve the powder; do not invert, swirl, or shake. Reconstitution of the lyophilised powder typically takes 2 minutes.

4

Perform an inspection of the reconstituted vials for particulate matter and discolouration. The reconstituted volume appears as a colourless-to-pale-yellow solution, clear to opalescent, and appears almost free of particles but may contain white-to-translucent particles.

- If upon immediate inspection foreign matter is observed, or if the solution is discoloured, do not use
- Each reconstituted vial should yield a concentration of 15 mg/mL with an extractable volume of 7.0 mL

5 Repeat the above steps for the number of vials needed for dilution.

5.7 Diluting the solution

Before dilution, select an intravenous (IV) bag with sufficient volume to achieve a final target concentration range of 0.5 mg/mL to 4 mg/mL for the diluted cipaglucosidase alfa solution for IV infusion.

Remove airspace within the infusion bag. Remove an equal volume of sodium chloride 9 mg/mL (0.9%) solution for injection that will be replaced by the total volume (mL) of reconstituted cipaglucosidase alfa.

Slowly withdraw the reconstituted solution from the vials until the patient's dose is obtained. Avoid foaming in the syringe. Discard any remaining reconstituted solution in the last vial.

Slowly inject reconstituted cipaglucosidase alfa. directly into the sodium chloride 9 mg/mL (0.9%) solution for injection bag. Do not add directly into the air space that may remain within the infusion bag.

- Gently invert or massage the bag to mix the diluted solution.
- Do not shake or excessively agitate the bag for infusion
- Do not use a pneumatic tube to transport the infusion bag

Cipaglucosidase alfa should be administered as stated below

- An intravenous administration set should be used with an inline low protein binding 0.2 micron filter. If the intravenous line blocks during infusion, change the filter.
- If immediate use is not possible, the reconstituted solution may be stored for up to 24 hours under refrigeration at 2°C to 8°C, followed by 6 hours at room temperature (20°C to 25°C) to allow for infusion.

5.8 Administering the infusion

Now you're ready to begin the infusion
The infusion will take approximately 4 hours.

1. The infusion solution should be administered at room temperature (between 20–25°C).
2. Total volume of infusion is determined by body weight and typically administered over approximately 4 hours.
3. Infusion of cipaglucosidase alfa should start approximately **1 hour after oral administration of miglustat.**
4. In the event of infusion delay, the **start of infusion should not exceed 3 hours from the oral administration of miglustat.**
5. The initial infusion rate should be no more than 1 mg per kg per hour for 30 minutes.
6. The infusion rate may be increased by 2 mg per kg per hour every 30 minutes, after patient tolerance to the infusion rate is established, until a maximum rate of 7 mg per kg per hour is reached.
7. Vital signs should be obtained at the end of each step.

Recommended Infusion Volumes and Rates

Patient Weight Range (kg)	**Total infusion volume** (mL)	**Step 1** 1 mg/kg/hr (mL/hr)	**Step 2** 1 mg/kg/hr (mL/hr)	**Step 3** 1 mg/kg/hr (mL/hr)	**Step 4** 1 mg/kg/hr (mL/hr)
40 – 50	**250**	13	38	63	88
50.1 – 60	**300**	15	45	75	105
60.1 – 100	**500**	25	75	125	175
100.1 – 120	**600**	30	90	150	210
120.1 – 140	**700**	35	105	175	245
140.1 – 160	**800**	40	120	200	280
160.1 – 180	**900**	45	135	225	315
180.1 – 200	**1000**	50	150	250	350

The infusion rate may be slowed or temporarily stopped in the event of mild-to-moderate IARs. In the event of severe allergic reaction or anaphylaxis, immediately stop the infusion and initiate appropriate medical treatment.

6 RECOGNISING AND MANAGING INFUSION-RELATED REACTIONS AND HYPERSENSITIVITY REACTIONS

An understanding of terms used to define the intensity (severity) of an adverse reaction may be useful.

- In general, a mild adverse reaction is one that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- A moderate adverse reaction is one that is sufficiently discomforting to interfere with normal everyday activities. A severe adverse reaction is one that prevents normal everyday activities. The term “severe” should not be confused with “serious.”
- “Severe” is used to describe the intensity (severity) of a specific event (mild, moderate or severe); the event itself, however, may be of relatively minor medical significance (such as severe headache).

Infusion-related reactions and hypersensitivity reactions

Infusion-related reactions (IARs) and hypersensitivity reactions have been known to occur during or up to a few hours after the infusion of cipaglucosidase alfa and other enzyme replacement therapies (ERTs). Most IARs reported with cipaglucosidase alfa were mild or moderate in severity and transient in nature, and included abdominal distension, chills, dizziness, dysgeusia, dyspnoea, flushing, pruritus, pyrexia, and rash. Severe IARs, such as anaphylaxis, have also been reported in patients treated with cipaglucosidase alfa. Symptoms of severe IARs may include angioedema, bronchospasm, chest pain, chills, dyspnoea, generalised hives, hypotension (feeling faint, paleness), laryngeal oedema, syncope and tachycardia.

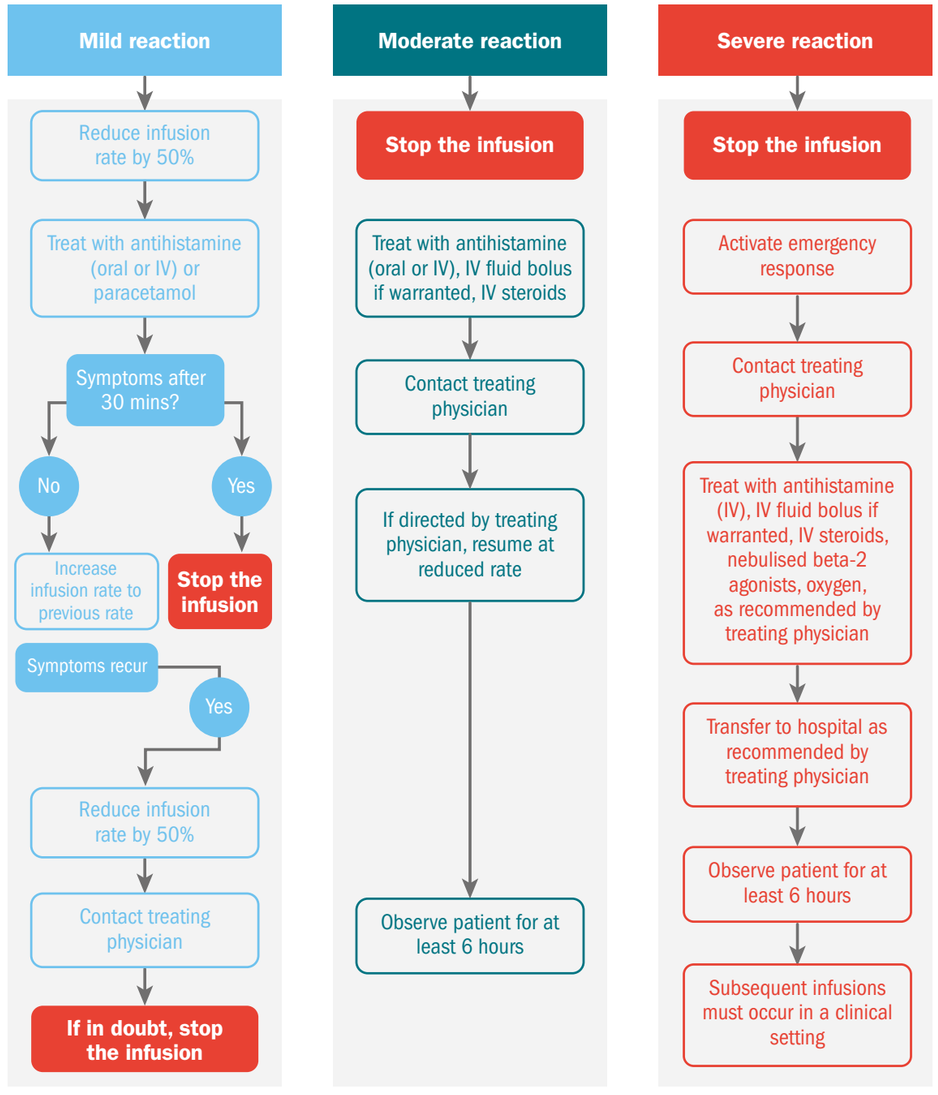
Management of infusion-related reactions

Reduction of the infusion rate, temporary interruption of the infusion, symptomatic treatment with oral antihistamine, or antipyretics, and appropriate resuscitation measures should be considered to manage IARs. In the event of a severe IAR, the infusion health professional/nurse must immediately pause the infusion and initiate appropriate medical treatment. The current medical standards for emergency treatment of anaphylactic reactions are to be observed and cardiopulmonary resuscitation equipment should be readily available.

The risks and benefits of re administering cipaglucosidase alfa following anaphylaxis or severe infusion reaction should be carefully considered, and if the patient continues therapy, their next infusion must occur in a clinical setting, equipped to deal with such medical emergencies.

CIPAGLUCOSIDASE ALFA + MIGLUSTAT RISK MINIMISATION **GUIDE FOR HEALTHCARE PROFESSIONALS**

The flowchart below presents recommendations on how to proceed in the event of an IAR. The recommendations for treatment given in the flow chart are only a suggestion. The treating physician makes a final decision regarding treatment in the emergency plan. Ensure immediate readiness for resuscitation before the start of the infusion. Record on infusion diary all details regarding times, adverse reactions, medications and infusion rates.



Please also refer to the current Summary of Product Characteristics (SmPC) for complete information on the safety of cipaglucosidase alfa, available at **www.medicines.org.uk/emc/product/14898**

7 REPORTING OF POTENTIAL ADVERSE REACTIONS

Post-authorisation reporting of suspected adverse reactions is important. It allows continuous monitoring of the benefit/risk balance of the medicinal product.

The treating physician or home infusion healthcare professional/nurse should report any suspected adverse reactions to Amicus Therapeutics via telephone on **0808 234 6864** or via e-mail to **drugsafety@amicusrx.com**.

Healthcare professionals are also asked to report any suspected adverse reactions using the Yellow Card Scheme via **www.mhra.gov.uk/yellowcard** or by searching for MHRA Yellow Card in the Google Play or Apple App Store.

If the patient or caregiver becomes aware that a mistake was made in the preparation and/or administration of the drug, the patient or infusion healthcare professional/nurse should inform the treating physician to determine appropriate action.

The treating physician or infusion healthcare professional/nurse should report any medication error as a spontaneous report to Amicus Therapeutics via telephone on **0808 234 6864** or via e-mail to **drugsafety@amicusrx.com**.

Healthcare professionals are also asked to report any suspected adverse reactions using the Yellow Card Scheme via **www.mhra.gov.uk/yellowcard** or by searching for MHRA Yellow Card in the Google Play or Apple App Store.

Pompe Disease registry

Healthcare professionals are asked to consider registering patients in the Amicus Pompe Disease registry by emailing: **info@amicusrx.co.uk**.

8 FURTHER INFORMATION

Please refer to the prescribing information for cipaglucosidase alfa and for miglustat for complete information on the safety and approved use of cipaglucosidase alfa in combination with miglustat.

The SmPC for cipaglucosidase alfa and the SmPC for miglustat are available on the EMC website, for cipaglucosidase alfa: **www.medicines.org.uk/emc/product/14898** and for miglustat: **www.medicines.org.uk/emc/product/14904**

Alternatively, the prescribing information can be requested at Amicus Therapeutics on **Tel: 01753 888 567**

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