PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]POMBILITI®

cipaglucosidase alfa for injection

Recombinant human acid α-glucosidase produced in Chinese hamster ovary cells [CHO]

Lyophilized Powder, 105 mg/vial, Intravenous infusion

Other alimentary tract and metabolism products, enzymes

Amicus Therapeutics Canada Inc.
100 King Street West, Suite 1600
1 First Canadian Place
Toronto ON M5X 1G5
Canada

Imported and Distributed by:
Innomar Strategies
8030 Esquesing Line
Milton, ON
L9T 6W3

Date of Authorization:
2025-04-14

Submission Control Number: 284815

RECENT MAJOR LABEL CHANGES

None at the time of the most recent authorization	

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

POMBILITI® (cipaglucosidase alfa for injection) is indicated:

- in combination with the enzyme stabiliser OPFOLDA (65 mg miglustat capsule) for the treatment of adult patients with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency) weighing ≥ 40 kg.

POMBILITI must be used in combination with 65 mg miglustat capsules. Consult the Product Monograph of OPFOLDA (65 mg miglustat capsule) for detailed information.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Limited evidence from clinical studies suggests that use of POMBILITI in combination with 65 mg miglustat capsules in the geriatric population is not associated with differences in safety or effectiveness (see 4.2 Recommended Dose and Dosage Adjustment, 7.1.4 Geriatrics, and 10.3 Pharmacokinetics).

2 CONTRAINDICATIONS

POMBILITI in combination with 65 mg miglustat capsule is contraindicated in:

- Patients with a history of life-threatening hypersensitivity or infusion-associated reactions (IARs) (e.g., anaphylaxis and severe cutaneous reactions) to cipaglucosidase alfa, or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container when rechallenge was unsuccessful (see 7 WARNINGS AND PRECAUTIONS, Immune, Anaphylaxis and Infusion Associated Reactions). For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients with a contraindication to 65 mg miglustat capsule including:
    - Patients who are hypersensitive to miglustat or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, refer to the Product Monograph of OPFOLDA (65 mg miglustat capsule)
    - Women who are or may become pregnant. If POMBILITI in combination with 65 mg miglustat capsules are administered to women of reproductive potential, they should be informed of the potential hazard to the fetus. Refer to the Product Monograph of OPFOLDA (65 mg miglustat capsule) (see 7.1.1 Pregnancy).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Hypersensitivity Reactions Including Anaphylaxis

- Patients treated with POMBILITI have experienced life-threatening hypersensitivity reactions, including anaphylaxis. Appropriate medical support measures, including cardiopulmonary

resuscitation equipment, should be readily available during POMBILITI administration. If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, infusion should be immediately paused, appropriate medical treatment initiated, and the benefits and risks of re-administration of POMBILITI should be considered (see 7 WARNINGS AND PRECAUTIONS).

Infusion-Associated Reactions (IARs)

- Patients treated with POMBILITI have experienced severe IARs. If severe IARs occur, infusion should be immediately paused, appropriate medical treatment initiated, and the benefits and risks of re-administration of POMBILITI should be considered following severe IARs (see 7 WARNINGS AND PRECAUTIONS).

Risk of Acute Cardiorespiratory Failure in Susceptible Patients

- 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 compromise due to fluid volume overload during POMBILITI infusion. Appropriate medical support and monitoring measures should be readily available during POMBILITI infusion (see 7 WARNINGS AND PRECAUTIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

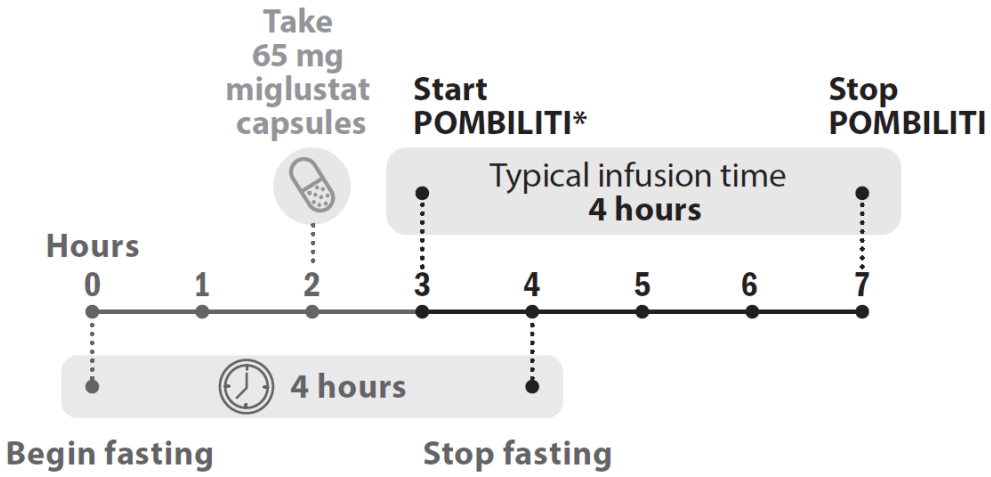
- POMBILITI must be used in combination with 65 mg miglustat capsules. Refer to the Product Monograph of OPFOLDA (65 mg miglustat capsule) prior to reconstituting POMBILITI for the number of capsules (based on body weight), dose time, fasting, and dose adjustments for patients with renal impairment.
- Verify the pregnancy status of female patients of reproductive potential prior to initiating POMBILITI in combination with 65 mg miglustat capsules (see 2 CONTRAINDICATIONS and 7.1.1 Pregnancy).
- Premedication and/or treatment during infusion with corticosteroids, oral antihistamines, and antipyretics may be administered to assist with signs and symptoms related to IARs (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS).
- Patient response to treatment should be routinely evaluated based on a comprehensive evaluation of all clinical manifestations of the disease. In the case of an insufficient response or intolerable safety risks, discontinuation of POMBILITI in combination with 65 mg miglustat capsules treatment should be considered (see 7 WARNINGS AND PRECAUTIONS). Both medicinal products should either be continued or discontinued together.
- Vials are single-use only. Any unused product should be discarded.

4.2 Recommended Dose and Dosage Adjustment

POMBILITI must be used in combination with 65 mg miglustat capsule. Refer to the Product Monograph of OPFOLDA (65 mg miglustat capsule) for detailed information on dosage and administration recommendations for 65 miglustat capsules.

The recommended dose of POMBILITI is 20 mg/kg body weight administered every other week as an intravenous infusion over approximately 4 hours (see 4.4 Administration). The POMBILITI infusion should start 1 hour after taking 65 mg miglustat capsules (see Figure 1 for the dosing timeline). In the event of infusion delay, the start of infusion should not exceed 3 hours from taking miglustat.

Figure 1 - Dose Timeline



* In the event of POMBILITI infusion delay, the start of infusion should not exceed 3 hours from taking 65 miglustat capsules.

Switching patients from another enzyme replacement therapy (ERT)

If the patient is switching from another ERT to POMBILITI in combination with 65 mg miglustat capsules therapy, the patient can be started with POMBILITI-miglustat therapy at the next scheduled dosing time (i.e., approximately 2 weeks after the last ERT administration).

Patients who have switched from another ERT to the POMBILITI-miglustat therapy should be advised to continue with any premedications used with the previous ERT therapy to minimise IARs. Depending on tolerability, premedication may be modified.

Patients with renal and hepatic impairment

The safety and efficacy of POMBILITI in combination with 65 mg miglustat capsules therapy have not been evaluated in patients with renal and/or hepatic impairment and no specific dose adjustments for POMBILITI can be recommended for these patients.

Refer to the Product Monograph of OPFOLDA (65 mg miglustat capsule) for the effects of renal impairment on miglustat exposures and miglustat dosage reduction recommendations in patients with moderate or severe renal impairment.

Geriatric use (≥65 years)

No dose adjustment is required for patients ≥65 years of age (see 10.3 Special Populations and Conditions -Geriatrics).

Pediatric use (<18 years)

Health Canada has not authorized an indication for pediatric use (see 1 INDICATIONS).

4.3 Reconstitution

Preparation before the infusion

- Use aseptic technique.
- Each vial of POMBILITI is for single-use only.

Calculating the dose

Determine the number of POMBILITI vials to be reconstituted based on patient's body weight.

1. Patient's body weight (kg) x dose (mg/kg) = Patient dose (mg)
2. Patient's dose (in mg) divided by 105 (mg per vial) = Number of vials to reconstitute
    - If the number of vials includes a fraction, round up to the next whole number.
    - Each reconstituted vial has a **concentration of 15 mg/mL** with an extractable volume of 7.0 mL.

Example: in a 65 kg patient dosed at 20 mg/kg

- Patient dose (mg): 65 kg x 20 mg/kg = 1300 mg total dose
- Number of vials to reconstitute: 1300 divided by 105 mg per vial = 12.38 vials and **round up** to 13 vials.
- Remove 7 mL from each of the first 12 vials.
  0.38 vial x 7.0 mL = 2.66 mL rounded to 2.7 mL from the 13th vial.

Items needed for reconstitution and dilution

- POMBILITI 105 mg vials
- Sterile water for injection at room temperature of 20°C to 25°C
- Sodium chloride 9 mg/mL (0.9%) for injection at room temperature of 20°C to 25°C
  Note: Choose a bag size(s) sufficient to dose based on the patient's body weight
- A needle of **18 gauge or lesser diameter**
- Do not use filter needles during preparation

Activities before reconstitution

- POMBILITI vials should be removed from the refrigerator (2°C to 8°C) and allowed to come to room temperature (i.e., approximately 30 minutes at 20°C to 25°C).
- Do not use if the vial is chipped, cracked, has fluid, lyophilized powder is discolored, closure is damaged, or button of overseal is removed.

Reconstituting the lyophilized powder

1. 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 lyophilized powder. Avoid forceful impact of sterile water for injection on the lyophilized powder and avoid foaming.
2. Tilt and roll each vial gently to dissolve the powder. Do not invert, swirl, or shake. Reconstitution of the lyophilized powder typically takes 2 minutes.
3. Perform an inspection of the reconstituted vials for particulate matter and discoloration. The reconstituted volume appears as a colorless to slightly yellow solution, clear to opalescent, and appears practically free of particles in the form of white to translucent visible particles in a vial. If upon immediate inspection, foreign matter is observed or if the solution is discolored, do not use.
4. Repeat above steps for the number of vials needed for dilution.

Table 1 - Reconstitution

Vial Size	Volume of Sterile Water for Injection to be Added to Vial	Approximate Available Volume	Concentration per mL
20 mL	7.2 mL	7.0 mL	15 mg/mL

The reconstituted solution is stable for up to 24 hours refrigerated at 2°C to 8°C. Storage at room temperature is not recommended (see 11 STORAGE, STABILITY AND DISPOSAL).

Dilution and preparation of the infusion

1. Select an intravenous 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.
2. Remove airspace within an infusion bag. Remove an equal volume of sodium chloride 9 mg/mL (0.9%) solution for injection that will be replaced by the volume (mL) of reconstituted cipaglucosidase alfa needed for the bag. Slowly withdraw 7 mL of the reconstituted solution from the vials, including less than 7 mL for the partial vial, until the patient's dose is obtained. Avoid foaming in the syringe. Discard any remaining reconstituted solution in the last vial.
3. Slowly inject the 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.
4. Gently invert or massage the bag to mix the diluted solution to prevent foaming. Do not shake or excessively agitate the bag for infusion. Do not use a pneumatic tube to transport the infusion bag.
5. Repeat steps on remaining infusion bag(s) to achieve the total volume (mL) of reconstituted cipaglucosidase alfa required for the patient's dose.

The infusion solution should be administered as close to after dilution preparation as possible at room temperature (see 4.4 Administration).

Preparing for administration

If it is not possible to start the infusion following dilution, the diluted solution is stable for up to 24 hours refrigerated at 2°C to 8°C, followed by up to 6 hours at room temperature, refer to the in-use stability storage conditions (see 11 STORAGE, STABILITY AND DISPOSAL). Do not freeze or shake.

The normal saline bag for infusion containing cipaglucosidase alfa is administered using an infusion pump.

Prior to infusion, inspect the infusion bag for foaming and if foaming is present, let foaming dissipate. Avoid shaking and handle infusion bag gently to prevent foaming.

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.

Other medicines should not be infused in the same intravenous line as the diluted cipaglucosidase alfa solution.

4.4 Administration

POMBILITI is to be administered by intravenous infusion.

Infusion can be administered in all sites of patient care including at home, in-clinic, and in hospital after comprehensive evaluation of IAR risks under the supervision of a healthcare professional (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS).

The total volume of infusion is determined by the patient's body weight. Infusion of the 20 mg/kg dose is normally administered over the course of 4 hours if tolerated. Infusion should be administered in a stepwise manner. The initial infusion rate should be no more than 1 mg/kg/hr for 30 minutes. The infusion rate may be increased by 2 mg/kg/hr every 30 minutes if there are no signs of IARs until a maximum rate of 7 mg/kg/hr is reached. Vital signs should be obtained at the end of each step. The infusion rate may be slowed or temporarily stopped in the event of mild to moderate infusion-associated reactions (IARs). In the event of severe allergic reaction, anaphylaxis, serious or severe IARs, immediately stop the infusion, and appropriate medical treatment should be initiated (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS).

Home infusion

Infusion of POMBILITI at home may be considered for patients after evaluation and upon recommendation by the treating healthcare professional (see 7 WARNINGS AND PRECAUTIONS).

The treating healthcare professional should be consulted if the patient experiences significant infusion reactions or if changes to recommended dose and/or infusion rate are required.

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

- The patient must have no ongoing concurrent condition that, in the opinion of the physician, may affect patient's ability to tolerate the infusion.
- The patient is considered medically stable. A comprehensive evaluation must be completed before the initiation of home infusion.
- The patient must have received POMBILITI infusions for a few months that could be in a hospital or in another appropriate setting of outpatient care. Documentation of a pattern of well-tolerated infusions is a prerequisite for the initiation of home infusion.
- The patient must be willing and able to comply with home infusion procedures.
- Home infusion infrastructure, resources, and procedures, including training, must be established and available to the home infusion staff. The home infusion staff should be available during the home infusion and for a specified time after infusion, depending on the patient's tolerance prior to starting home infusion.
- For patients switching to POMBILITI from another ERT, it is recommended that the first infusions of POMBILITI occur in a hospital/clinic setting due to the risk of infusion associated reactions.

If the patient experiences adverse reactions during the home infusion, the infusion process should be stopped immediately, and appropriate medical treatment should be initiated (see 7 WARNINGS AND PRECAUTIONS). Subsequent infusions may need to occur in a hospital or in an appropriate setting of outpatient care until no such adverse reaction is present. Dose and infusion rate must not be changed without consulting the responsible healthcare professional.

Patients and/or caregivers must be informed about the risks associated with home infusion of POMBILITI and receive proper education on managing severe infusion-associated reactions. This includes understanding necessary actions and emergency contact details, which should be documented in the patient's infusion diary. Educational risk materials for home infusion are available through the manufacturer.

4.5 Missed Dose

If the 65 mg miglustat capsules dosage is missed, do not start the POMBILITI infusion. If the POMBILITI infusion cannot be started within 3 hours of oral administration of 65 mg miglustat capsules, reschedule treatment of 65 mg miglustat capsules and POMBILITI at least 24 hours after taking 65 mg miglustat capsules. If POMBILITI and 65 mg miglustat capsules are both missed, treatment should occur as soon as possible. These 2 medicines should be administered at the next available opportunity when they can be given as detailed in Figure 1.

5 OVERDOSAGE

There is no experience with overdose of POMBILITI and/or 65 mg miglustat capsules.

In the event of an overdose, supportive medical care should be administered immediately including consulting with a healthcare professional and close observation of the clinical status of the patient.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of **biologic products**, including biosimilars, healthcare professionals should record both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 2 - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	Lyophilized powder, 105 mg/vial	Citric acid monohydrate, mannitol, polysorbate 80, sodium citrate dihydrate

One 20 mL vial contains 105 mg of cipaglucosidase alfa.

POMBILITI is a white to slightly yellowish lyophilized powder. It is supplied in a neutral borosilicate clear glass vial sealed with a 20 mm chlorobutyl rubber stopper and with an aluminum overseal with a dark grey flip-off cap.

Packs contain 1, 10, or 25 vials.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

POMBILITI must be administered in combination with 65 mg miglustat capsules. Refer to the Product Monograph of OPFOLDA (65 mg miglustat capsule) for a description of additional risks for 65 mg miglustat capsules including, but not limited to, the warnings and precautions for 65 mg miglustat capsules.

Cardiovascular

Risk of acute cardiorespiratory failure in susceptible patients

Patients susceptible to fluid volume overload, or those with acute underlying respiratory illness or compromised cardiac and/or respiratory function for whom fluid restriction is indicated, may be at risk of serious exacerbation of their cardiac or respiratory compromise during POMBILITI infusion. Appropriate medical support measures and more frequent monitoring should be readily available during POMBILITI infusion.

Driving and Operating Machinery

No studies on the effects on the ability to drive or to use machinery have been performed with POMBILITI in combination with 65 mg miglustat capsules. Since dizziness, hypotension, and somnolence have been reported as adverse reactions, POMBILITI in combination with 65 mg miglustat capsules may have minor influence on the ability to drive and use machines. Caution is required when driving or operating a vehicle or potentially dangerous machinery.

Immune

Hypersensitivity Reactions including Anaphylaxis

Life-threatening hypersensitivity reactions, including anaphylaxis, were reported in 1 (1.2 %) POMBILITI-treated patient from Phase 3 Clinical Trial (PROPEL). Premedication with oral antihistamine, antipyretics, and/or corticosteroids may be administered to assist with signs and symptoms related to hypersensitivity reactions experienced with prior ERT treatment. 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 serious hypersensitivity reactions.

If anaphylaxis or severe allergic reactions occur, infusion should be immediately paused, and appropriate medical treatment should be initiated. 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 POMBILITI following anaphylaxis or severe allergic reaction should be carefully considered, and appropriate resuscitation measures made available if the decision is made to readminister the medicinal product.

If a patient experiences anaphylaxis or severe allergic reactions in the home setting, and if the patient continues therapy, their next infusions must occur in a clinical setting equipped to deal with such medical emergencies.

Immune Complex-related Reactions

Immune complex-related reactions have been reported with other enzyme replacement therapies in patients who had high IgG antibody titres, including severe cutaneous reactions and nephrotic syndrome.

A potential class effect cannot be excluded. Patients should be monitored for clinical signs and symptoms of systemic immune complex-related reactions while receiving POMBILITI in combination with 65 mg miglustat capsules. If immune complex-related reactions occur, discontinuation of the administration of POMBILITI should be considered and appropriate medical treatment should be initiated. The risks and benefits of re-administering POMBILITI following an immune complex-related reaction should be considered.

Infusion-associated Reactions

In clinical trials, infusion associated reactions (IARs) were reported to occur at any time during and/or within a few hours after the POMBILITI infusion and were more likely to occur with higher infusion rates. IARs were reported in 48 (32%) POMBILITI-treated patients in clinical trials. Severe IARs included symptoms of pharyngeal edema, anaphylactic reaction, urticaria, pruritus, chills, dyspnea, and flushing. The majority of IARs were assessed as mild to moderate. IARs that led to treatment discontinuation were urticaria, anaphylactic reaction, chills, and hypotension.

Antihistamines, antipyretics, and/or corticosteroids can be given prior to POMBILITI administration to reduce the risk of IARs. However, IARs may still occur in patients after receiving premedication.

- If severe IARs occur, immediately discontinue the POMBILITI infusion, initiate appropriate medical treatment, and assess the benefits and risks of re-administering POMBILITI following severe IARs. Patients may be rechallenged using slower infusion rates. Once the patient tolerates the infusion, the infusion rate may be increased to the recommended infusion rate.
- If mild or moderate IARs occur, regardless of premedication slowing the infusion rate or temporarily stopping the infusion may improve symptoms; medical treatment or discontinuation of POMBILITI may not be required.

Patients with an acute underlying illness at the time of POMBILITI infusion may be at a greater risk for IARs. Patients with advanced Pompe disease may have compromised cardiac and respiratory function, which may predispose them to a higher risk of severe complications from IARs.

Reproductive Health

Advise women of childbearing potential to use effective contraception during treatment, and for 4 weeks after the last dose of POMBILITI in combination with 65 mg miglustat capsules. Based on findings from animal reproduction studies, POMBILITI in combination with miglustat may cause embryo-fetal harm when administered to a pregnant female and is contraindicated in women of childbearing potential not using reliable contraception (see 2 CONTRAINDICATIONS, 7.1.1 Pregnancy, and 16 NON-CLINICAL TOXICOLOGY).

Fertility

There are no clinical data on the effects of POMBILITI in combination with 65 mg miglustat capsules on fertility. For additional information about fertility with the use of 65 mg miglustat capsule, see the Product Monograph of OPFOLDA (65 mg miglustat capsule).

An increase in pre-implantation loss was noted with cipaglucosidase alfa in combination with miglustat, and with miglustat alone in reproductive and developmental toxicity studies in male rats

mated with untreated females and in females mated with untreated males. Based on pre-implantation loss observed in female and male rats, POMBILITI in combination with miglustat may impair human female and male fertility (see 16 NON-CLINICAL TOXICOLOGY).

Teratogenic Risk

Based on findings from animal reproduction studies, POMBILITI in combination with miglustat may cause embryo-fetal harm when administered to a pregnant female and is contraindicated during pregnancy (see 2 CONTRAINDICATIONS, 7.1.1 Pregnancy, and 16 NON-CLINICAL TOXICOLOGY). In a rabbit embryo-fetal development study, great vessel and cardiac malformations were increased in offspring of pregnant rabbits treated with cipaglucosidase alfa in combination with miglustat at 16-fold and 3-fold, respectively, the maximum recommended human dose (MRHD) based on plasma AUC exposure.

Monitoring and Laboratory Tests

Patients should be informed that a registry for patients with Pompe disease has been established to assess long-term safety and effectiveness of Pompe disease treatments. Patients should be encouraged to participate and be advised that their participation may involve long-term follow-up.

7.1 Special Populations

7.1.1 Pregnancy

POMBILITI in combination with 65 mg miglustat capsule is contraindicated during pregnancy due to its unknown potential risk for humans (see 2 CONTRAINDICATIONS). There are no clinical data for the use of POMBILITI in combination with 65 mg miglustat capsules in pregnant women. Cipaglucosidase alfa in combination with miglustat as well as with miglustat alone have shown reproductive and developmental toxicity in animal studies (i.e., rat and rabbit), including pre-implantation loss and clusters of great vessel and cardiovascular malformations in offspring (see 16 NON-CLINICAL TOXICOLOGY).

7.1.2 Breast-feeding

There are no data on the presence of POMBILITI alone or in combination with 65 mg miglustat capsules in human breast milk, the effects on the breastfed infant, or the effects on milk production. Available pharmacodynamic/toxicological data in animals have shown excretion of cipaglucosidase alfa in milk (see 16 NON-CLINICAL TOXICOLOGY). Because of a risk to the breast-feeding new-borns/infants that cannot be excluded, advise women that breast-feeding is not recommended while on treatment with POMBILITI in combination with 65 mg miglustat capsules.

7.1.3 Pediatrics

Pediatrics (< 18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

There is limited clinical data with POMBILITI in combination with 65 mg miglustat capsules in elderly patients. Limited data suggests that use of POMBILITI in combination with 65 mg miglustat capsules in the geriatric population is not associated with differences in safety or effectiveness. As clinical trials of POMBILITI in combination with miglustat did not include sufficient numbers of patients ≥ 65 years of age

treated with POMBILITI in combination with miglustat, no definitive conclusions can be drawn to determine whether they respond differently from younger adult patients. Of the total number of patients treated with POMBILITI in combination with miglustat in clinical trials for late-onset Pompe disease (LOPD), 17 (11%) subjects were 65 to 74 years of age, and none were 75 years of age and older.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common adverse reactions (≥ 5%) reported in POMBILITI in combination with miglustat treated subjects in all 3 studies were headache, diarrhoea, fatigue, nausea, abdominal pain, pyrexia, and chills.

Reported serious adverse reactions in all 3 studies were urticaria (2.0%), anaphylaxis (1.3%), chills (0.7%), cough (0.7%), flushing (0.7%), pyrexia (0.7%), presyncope (0.7%), dyspnoea (0.7%), pharyngeal oedema (0.7%), wheezing (0.7%), and hypotension (0.7%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trial may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in the clinical trials of another drug.

The pooled safety analysis from 3 clinical trials included 151 adult patients with LOPD treated with POMBILITI in combination with miglustat including:

- 85 patients in the randomized, double-blind, active-controlled trial in adults,
- 37 patients in the open-label extension trial where patients switched from an approved alglucosidase alfa product to POMBILITI in combination with miglustat,
- 29 patients in an open-label trial.

The assessment of adverse reactions was informed by subjects treated with POMBILITI in combination with miglustat across 3 clinical trials. The total mean duration of exposure was 28.0 months.

Phase 3 clinical trial (PROPEL) included 123 adult patients with LOPD who were randomized to receive treatment with POMBILITI in combination with miglustat or alglucosidase alfa in combination with placebo. Adverse reactions from the Phase 3 clinical trial (PROPEL) are listed by MedDRA system organ class in Table 3.

Table 3 - Summary of Adverse Reactions Reported in ≥ 2% of Patients in Phase 3 Clinical Trial (PROPEL)

	POMBILITI in Combination with Miglustat N = 85 n (%)	Alglucosidase alfa in Combination with Placebo N = 38 n (%)
Cardiac disorders		
Tachycardia‡4	2 (2.4%)	0
Gastrointestinal disorders		
Abdominal distension	3 (3.5%)	2 (5.3%)**
Abdominal pain‡1	2 (2.4%)	4 (10.5%)
Diarrhoea	5 (5.9%)	2 (5.3%)**
Nausea	2 (2.4%)**	5 (13.2%)
General disorders and administration site conditions		
Chills	2 (2.4%)*	0
Pyrexia	3 (3.5%)	1 (2.6%)*
Musculoskeletal and connective tissue disorders		
Muscle spasms	2 (2.4%)	0
Nervous system disorders		
Dizziness	4 (4.7%)*	2 (5.3%)*
Dysgeusia	2 (2.4%)	0
Headache‡5	7 (8.2%)	3 (7.9%)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	3 (3.5%)	0
Skin and subcutaneous tissue disorder		
Pruritus	2 (2.4%)*	2 (5.3%)
Rash‡2	3 (3.5%)*	0
Urticaria‡3	2 (2.4%)*	0
Vascular disorders		
Flushing	2 (2.4%)*	0

* Related to POMBILITI/alglucosidase alfa only

** Related to miglustat/Placebo only

‡ Adverse reactions that are medically related were grouped to a single preferred term.

1 Abdominal pain, abdominal pain upper, and abdominal pain lower are grouped under abdominal pain.

2 Rash, rash erythematous and rash macular are grouped under rash.
3 Urticaria, mechanical urticaria, and urticaria rash are grouped under urticaria.
4 Tachycardia and sinus tachycardia are grouped under tachycardia.
5 Headache, migraine, and migraine with aura are grouped under headache.

Infusion-Associated reactions (IARs)

The following IARs were reported in at least 2 subjects in the Phase 3 clinical trial (PROPEL) during the POMBILITI infusion or within 2 hours after completion of the infusion: abdominal distension, chills, pyrexia, dizziness, dysgeusia, dyspnea, pruritus, rash, and flushing.

0.7% of patients experienced a serious adverse reaction of anaphylaxis (characterized by generalised pruritus, dyspnea, and hypotension) during the PROPEL study receiving POMBILITI and miglustat. 1.3% of patients receiving POMBILITI and miglustat discontinued treatment due to IARs (anaphylaxis and chills). Most IARs were mild or moderate in severity, transient in nature and none were assessed as life--threatening or fatal. Most subjects who experienced IARs were able to continue treatment with POMBILITI in combination with miglustat.

8.3 Less Common Clinical Trial Adverse Reactions

Adverse reactions from the clinical trials reported in less than 2% of patients from pooled analysis of 3 clinical trials were:

Gastrointestinal disorders: abdominal discomfort†, constipation†, dyspepsia*, oesophageal pain*, oesophageal spasm, oral discomfort*, oral pain, swollen tongue*

General disorders and administration site conditions: asthenia, chest discomfort*, facial pain, feeling jittery†, infusion site pain*, infusion site swelling*, malaise*, non-cardiac chest pain, pain*, peripheral swelling, swelling face*

Immune system disorders: anaphylactic reaction‡2, hypersensitivity

Injury, poisoning and procedural complications: skin abrasion*

Investigations: body temperature fluctuation*, lymphocyte count decreased, platelet count decreased†

Musculoskeletal and connective tissue disorders: arthralgia, flank pain, muscle fatigue, muscular weakness, musculoskeletal stiffness

Nervous system disorders: balance disorder, burning sensation*, dysgesusia, migraine‡1, paraesthesia, presyncope*

Respiratory, thoracic and mediastinal disorders: asthma, cough*, oropharyngeal discomfort*, pharyngeal oedema*, wheezing*

Skin and subcutaneous tissue disorder: skin discolouration, skin oedema*

Vascular disorders: hypotension, pallor

* Related to cipaglucosidase alfa only; † Related to miglustat only; ‡ Adverse reactions that are medically related were grouped to a single preferred term; 1 Migraine and migraine with aura are grouped under migraine; 2 Anaphylactic reaction, Anaphylaxis are grouped under Anaphylactic reaction. Anaphylactoid reaction is manually coded to Anaphylaxis.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

There were no clinically significant abnormal laboratory findings with POMBILITI in combination with miglustat in the clinical studies.

8.5 Post-Market Adverse Reactions

No new safety findings which alter the safety profile of POMBILITI in combination with miglustat have been observed post-marketing.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No interaction studies have been performed using POMBILITI or with POMBILITI in combination with miglustat.

9.3 Drug-Behaviour Interactions

The interaction of POMBILITI or POMBILITI in combination with miglustat with individual behavioural risks (e.g. cigarette smoking, cannabis use, and/or alcohol consumption) has not been studied.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

Refer to the Product Monograph of OPFOLDA (65 mg miglustat capsule) for miglustat-food interactions and fasting instructions.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Pompe disease (acid maltase deficiency, glycogen storage disease type II [GSD II], glycogenosis type II) is a rare metabolic myopathy caused by a deficiency of acid alpha-glucosidase (GAA) enzyme that degrades glycogen in the lysosome. GAA deficiency leads to progressive accumulation of intra lysosomal glycogen, defective autophagy, and disruption of cellular function, primarily in cells of smooth, cardiac, and skeletal muscle.

Cipaglucosidase alfa is a hydrolytic glycogen-specific enzyme intended to replace absent or impaired endogenous GAA enzyme. Cipaglucosidase alfa contains the mammalian cell line [Chinese Hamster Ovary (CHO)] derived bis-M6P N-glycans for high affinity cation-independent mannose-6-phosphate receptor (CI-MPR) binding. After binding, it is internalised in the lysosome where it undergoes proteolytic cleavage and N-glycan trimming necessary to produce mature form of the enzyme. Cipaglucosidase alfa is stabilised by miglustat, minimising the loss of enzyme activity in the blood during infusion.

10.2 Pharmacodynamics

In the Phase 3 trial, PROPEL, subjects treated with 20 mg/kg cipaglucosidase alfa in combination with miglustat (n = 84) showed a mean reduction of -31.5% (95% CI: -38.3%, -24.8%) in urinary glucose tetrasaccharide (Hex-4) after 52 weeks. The exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of POMBILITI have not been fully characterized.

10.3 Pharmacokinetics

Table 4 - Summary of Cipaglucosidase alfa Pharmacokinetic Parameters in ambulatory ERT-experienced LOPD Patients

	C_{max}[a] (µg/mL)	T_{max}[b] (h)	$t_{½}$[c] (h)	$AUC_{0-\infty}$[a] (µg·h/mL)	CL_T[c] (L/h)	V_{ss}[c] (L)
Cipaglucosidase alfa 20 mg/kg alone (n = 11)	325 (13.5)	4.00 (3.5 - 4.0)	2.3 (38.7)	1410 (15.9)	1.27 (17.8)	3.65 (12.0)
Cipaglucosidase alfa 20 mg/kg + miglustat 260 mg (n = 11)	345 (18.5)	3.90 (3.4 - 4.0)	2.6 (19.2)	1812 (20.8)	0.991 (22.4)	3.65 (15.8)

Abbreviations: $AUC_{0-\infty}$ = area under the curve from 0 to infinity; CL_T = total clearance following intravenous administration; C_{max} = maximum observed plasma concentration; t½ = half-life; T_{max} = time to reach the maximum observed concentration; V_{ss} = volume of distribution at steady state

[a] Geometric mean (CV%)
[b] Median (Min - Max)
[c] Arithmetic mean (CV%)

Absorption

The maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) of cipaglucosidase alfa following administration with 20 mg/kg of cipaglucosidase alfa in combination with a single oral dose of 260 mg of miglustat in adult patients with LOPD are summarized in Table 4.

Distribution

Following administration of a single dose of 260 mg miglustat in combination with 20 mg/kg cipaglucosidase alfa in fasting adults with Pompe disease in a Phase 1/2 study, total GAA protein partial $AUC_{tmax-24h}$ (area under the plasma concentration-time curve from the time to reach maximum observed plasma concentration to 24 hours after the start of infusion) increased by 44% relative to 20 mg/kg cipaglucosidase alfa alone.

The mean volume of distribution of 20 mg/kg of cipaglucosidase alfa with a single oral dose of 260 mg of miglustat in adult patients with LOPD are summarized in Table 4.

Metabolism

The metabolic pathway of cipaglucosidase alfa has not been characterized. Cipaglucosidase alfa is expected to be metabolized into small peptides and amino acid via catabolic pathways.

Elimination

The mean elimination half-life ($t_{1/2}$) for 20 mg/kg of cipaglucosidase alfa with a single oral dose of 260 mg miglustat in adult patients with LOPD are summarized in Table 4.

Special Populations and Conditions

- **Pediatrics:** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.
- **Geriatrics:** Based on the limited experience with the use of cipaglucosidase alfa in combination with miglustat therapy in patients above the age of 65 years old and a pooled population pharmacokinetic analysis, no dose adjustment is recommended in elderly patients.
- **Sex:** Based on a pooled population pharmacokinetic analysis, sex did not have a clinically meaningful effect on cipaglucosidase alfa exposure in combination with miglustat.
- **Hepatic Insufficiency:** The pharmacokinetics of cipaglucosidase alfa in combination with miglustat have not been evaluated in patients with hepatic impairment.
- **Renal Insufficiency:** The pharmacokinetics of cipaglucosidase alfa in combination with miglustat have not been evaluated in patients with renal impairment. Refer to the Product Monograph of OPFOLDA (65 mg miglustat capsule) for the effects of renal impairment on miglustat exposures and miglustat dosage reduction recommendations in patients with moderate or severe renal impairment.

10.4 Immunogenicity

All therapeutic proteins have the potential for immunogenicity.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies in the studies described below with the incidences of antibodies in other studies or to other products may be misleading.

Table 5 presents the incidence of antidrug antibodies (ADA) and neutralizing antibodies against cipaglucosidase alfa in adult patients with LOPD treated with POMBILITI in combination with miglustat during the 52-week treatment period in Phase 3 trial (PROPEL).

Subjects who had an IAR post-treatment were tested for anti rhGAA IgE (immunoglobulin E) after the occurrence of the IAR; there was no clear trend in IAR occurrence with the incidence of anti rhGAA IgE.

Overall, there was no apparent association between immunogenicity and safety or pharmacokinetic effects; however, patients should be monitored for signs and symptoms of systemic immune complex-related reactions [see 7 WARNINGS AND PRECAUTIONS].

Table 5 ADA response in patients with LOPD in Phase 3 trial (PROPEL)

Antidrug Antibodies	ERT-experienced Patients (N = 65) n (%)	ERT-naïve Patients (N = 20) n (%)
ADA at Baseline	55 (85%)	3 (15%)
ADA at Week 52	58 (89%)	20 (100%)
Neutralizing antibodies at Week 52		
Inhibition of enzyme activity†	26 (40%)	4 (20%)
Inhibition of enzyme activity‡	24 (37%)	5 (25%)
Inhibition of CI-MPR binding§	53 (82%)	13 (65%)

N = Total number of subjects
n = number of subjects positive for anti-cipaglucosidase alfa antibodies
† Enzyme activity measured as 4-methylumbelliferone-α-D-glucopyranoside (4-MU-α-Glc) hydrolysis
‡ Enzyme activity measured as glycogen hydrolysis
§ Inhibition of cation independent mannose-6-phosphate receptor (CI-MPR) binding

11 STORAGE, STABILITY AND DISPOSAL

Store in original container or equivalent to protect from light.

Do not freeze. Store under refrigeration (2°C to 8°C).

Keep out of reach and sight of children.

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

In-use stability (after reconstitution and dilution)

Do not freeze the reconstituted vial or the diluted cipaglucosidase alfa solution in the bag for infusion.

From a microbiological point of view, the medicinal product should be used immediately and if not used immediately, the in-use storage times should not exceed those listed below.

Cipaglucosidase alfa reconstituted with sterile water for injection can be stored up to 24 hours when refrigerated at 2°C to 8°C. Storage at room temperature is not recommended.

The reconstituted vial diluted with sodium chloride solution for injection can be stored up to 24 hours when refrigerated at 2°C to 8°C, followed by up to 6 hours at room temperature (20°C to 25°C).

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

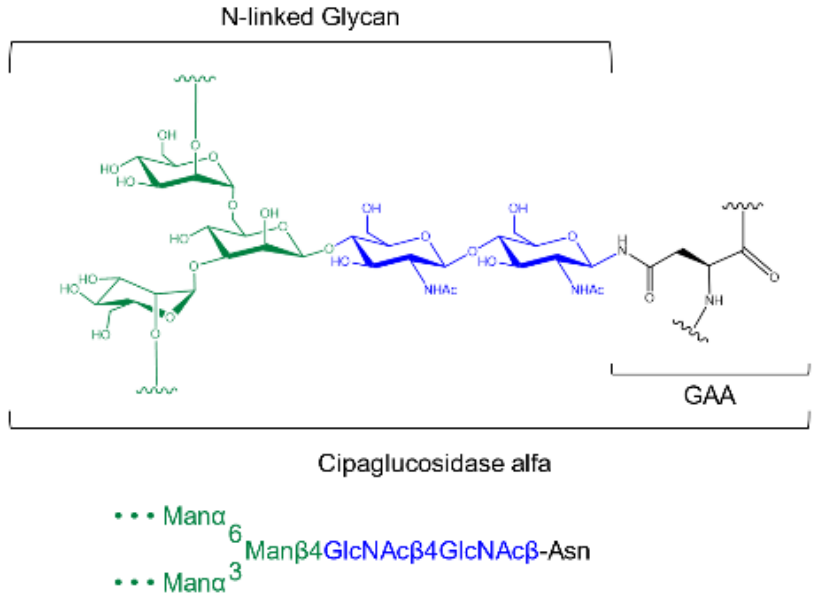
Proper name: cipaglucosidase alfa

Chemical name: recombinant human acid α-glucosidase

Molecular formula: $C_{4489}H_{6817}N_{1197}O_{1298}S_{32}$ (full length polypeptide)

Molecular mass: 110000 Da

Structural formula:



Physicochemical properties: Cipaglucosidase alfa is white to slightly yellowish lyophilized powder. After reconstitution, it appears as a colorless to slightly yellow solution, clear to opalescent, and appears practically free of particles in the form of white to translucent visible particles in a vial.

Product Characteristics:

Cipaglucosidase alfa is a hydrolytic glycogen-specific enzyme, produced by recombinant DNA methodology derived from Chinese Hamster Ovary (CHO) cell line using perfusion methodology, resulting in cellularly (CHO)-derived N-glycans. This genetic technology deliberately creates a recombinant enzyme with a very similar structure to the natural form of human acid α-glucosidase (rhGAA) enzyme. Cipaglucosidase alfa degrades glycogen by catalyzing the hydrolysis of α-1,4- and α-1,6-glycosidic linkages of lysosomal glycogen.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Table 6 - Summary of Patient Demographics for Clinical Trial in Late-onset Pompe Disease

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
ATB200-03 (PROPEL)	Multicenter, double-blind, randomized, active-controlled	20 mg/kg cipaglucosidase alfa IV + 195/260 mg miglustat oral capsules every other week Or 20 mg/kg alglucosidase alfa IV + placebo oral capsules every other week **Duration:** 52 weeks	123*	46.8 years (19 to 74 years)	Male: 56 Female: 67

* The Intent-to-Treat (ITT) population comprised 123 subjects. The efficacy population, excluding one outlier, consisted of 122 subjects. IV: intravenous

A 52-week Phase 3 randomized, double-blind, active-controlled, international, multi-center clinical trial was conducted in adult subjects (≥ 18 years) diagnosed with late-onset Pompe disease and weighing ≥ 40 kg. Subjects were randomized 2:1 to receive POMBILITI in combination with 65 mg miglustat capsules or alglucosidase alfa plus placebo every other week for 52 weeks. The efficacy population included a total of 122 subjects of which 95 (78%) had received prior ERT with alglucosidase alfa (ERT-experienced) and 27 (22%) had never received ERT (ERT-naïve).

Demographics, baseline 6-Minute Walk Distance (6MWD), and sitting percent predicted Forced Vital Capacity (FVC) were representative of the population and generally similar in the 2 treatment arms. More than two thirds (67%) of ERT-experienced subjects had been on ERT treatment for more than 5 years prior to entering the PROPEL study (mean of 7.4 years).

Efficacy endpoints included assessment of motor function and pulmonary function.

Motor Function

6-Minute Walk Distance (6MWD) at 52 weeks

The efficacy results of 6MWD are summarized in Table 7.

ERT-experienced Vs. ERT-naïve patients:

The ERT-experienced subjects treated with POMBILITI in combination with 65 mg miglustat capsules (n = 65) had a mean improvement in walk distance from baseline to Week 52 of 16.5 meters as compared to a mean of 0.6 meters for alglucosidase alfa plus placebo (n = 30), indicating a POMBILITI in combination with 65 mg miglustat capsules treatment effect of 16.1 meters (95% CI: -0.1, 32.3).

The ERT-naïve subjects treated with POMBILITI in combination with 65 mg miglustat capsules (n = 20) had a mean improvement in walk distance from baseline to Week 52 of 33.4 meters as compared to 38.3 meters for alglucosidase alfa plus placebo (n = 7), indicating a POMBILITI in combination with 65 mg miglustat capsules treatment effect of –4.9 meters (95% CI: -45.4, 35.6).

Pulmonary Function

Sitting percent-predicted forced vital capacity (FVC) at 52 weeks

The efficacy results of FVC are summarized in Table 7.

ERT-experienced Vs. ERT-naïve patients:

The ERT-experienced subjects treated with POMBILITI in combination with 65 mg miglustat capsules (n = 64) showed a mean change in FVC from baseline to Week 52 of –0.6% as compared with subjects treated with alglucosidase alfa and placebo of –3.5% (n = 30), indicating a POMBILITI in combination with 65 mg miglustat capsules treatment effect of 2.9% (95% CI: 0.5%, 5.3%).

The ERT-naïve subjects treated with POMBILITI in combination with 65 mg miglustat capsules (n = 20) showed a mean change in FVC from baseline to Week 52 of -5.2% as compared with subjects treated with alglucosidase alfa and placebo (n = 7) of -2.5%, indicating a POMBILITI in combination with 65 mg miglustat capsules treatment effect of -2.7% (95% CI: -9.1%, 3.9%).

Table 7 - Results of Key Endpoints at Duration 52 weeks in All Subjects from PROPEL Study*

	POMBILITI-miglustat (N = 85)	Alglucosidase alfa-placebo (N = 37)
Primary endpoint		
6MWD		
Baseline		
n	n = 85	n = 37
Mean (SD)	357.9 (111.8)	351.0 (121.3)
Median	359.5	365.5
Change from baseline at Week 52		
n	n = 85	n = 37
Mean (SD)	20.5 (41.3)	7.7 (40.0)
(95% CI)	(11.6, 29.4)	(-5.6, 21.1)
Median	12.7	1.4
Change to Week 52		
Diff. in LS means (SE)	13.1[a] (7.4)	
(95% CI)	(-1.5, 27.7)	
Key Secondary endpoint		
Sitting Percent Predicted FVC		
Baseline		
n	n = 85	n = 37
Mean (SD)	70.7 (19.6)	69.7 (21.5)
Median	70.0	71.0
Change from baseline at Week 52		
n	n = 84	n=37
Mean (SD)	-1.5 (6.0)	-3.7 (4.4)
(95% CI)	(-2.8, -0.2)	(-5.1, -2.2)
Median	-2.2	-3.6
Change to Week 52		
Diff. in LS means (SE)	2.1[b] (1.1)	
(95% CI)	(0.0, 4.3)	

Abbreviations: CI: confidence interval; Diff.: difference; LS: least square; SD: standard deviation; SE: standard error

* The value of one subject was an outlier and was excluded from the analysis.

[a] Missing values at Week 52 were imputed using the data from the control group. The treatment difference of the mean was estimated by non-parametric analysis of covariance which included treatment, gender, ERT status, baseline 6MWD, age, weight, and height in the model.

[b] Missing values at Week 52 were imputed using the data from the control group. The treatment difference of the mean was estimated by analysis of covariance which included treatment, gender, ERT status, baseline FVC, age, weight, and height in the model.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

In a 26-week repeat-dose toxicity study in rats, male and female rats were administered cipaglucosidase alfa once every other week for 26 weeks (13 doses) at 0 (vehicle), 30, 70, or 200 mg/kg by the IV route followed by a 4-week recovery period. No test article-related mortalities occurred in the study. Slight decrease in blood glucose (females) in the 70 and 200 mg/kg dose groups and slight increases in white blood cells (females), lymphocytes (females) and basophil counts (females) together with slight increase in calcium (male) in the 200 mg/kg dose were observed. Those changes were judged to be potentially related to treatment; however, these effects were not considered adverse or toxicologically significant because the magnitude of the changes was generally small and there were no relevant correlating changes in histopathology. The no observed adverse effect level (NOAEL) was 200 mg/kg, equivalent to a systemic exposure 15-fold greater than humans at the maximum recommended human dose (MRHD) of 20 mg/kg bw cipaglucosidase alfa with 260 mg miglustat, based on the mean sex-averaged $AUC_{0\text{-}t}$ (total cipaglucosidase alfa protein) of 21150 µg·h/mL at 200 mg/kg.

In a 26-week repeat-dose toxicity study in cynomolgus monkeys, males and females were administered cipaglucosidase alfa intravenously once every other week for 26 weeks (13 doses) at 0 (vehicle), 30, 60, or 200 mg/kg followed by a 4-week recovery period. No changes attributable to cipaglucosidase alfa administration were recorded. The NOAEL was 200 mg/kg, equivalent to systemic exposure 18-fold greater than in humans at the MRHD of 20 mg/kg bw cipaglucosidase alfa with 260 mg miglustat, based on the mean sex-averaged $AUC_{0\text{-}t}$ (total cipaglucosidase alfa protein) of 25000 µg·h/mL at 200 mg/kg.

In a 13-week repeat-dose toxicity study in cynomolgus monkeys, males and females were administered cipaglucosidase alfa intravenously both with and without orally-administered miglustat, once every other week for 13 weeks (7 doses). Dose groups consisted of combination doses (50 mg/kg cipaglucosidase alfa with 25 mg/kg miglustat, or 100 mg/kg cipaglucosidase alfa with 175 mg/kg miglustat), or 100 mg/kg cipaglucosidase alfa or 175 mg/kg miglustat administered alone. There were no changes attributable to cipaglucosidase alfa or miglustat or to their co-administration. The NOAEL for cipaglucosidase alfa in this study with or without miglustat co-administration was 100 mg/kg, the highest dose tested. At this dose level, systemic exposure is 6-fold and 10-fold human exposure at the MRHD based on the mean sex-averaged $AUC_{0\text{-}t}$ (total protein) levels for cipaglucosidase alfa alone or for cipaglucosidase alfa in combination with 175 mg/kg miglustat of 7810 µg·h/mL and 13850 µg·h/mL, respectively.

Genotoxicity

No studies have been performed to evaluate the genotoxic potential of cipaglucosidase alfa with or without co-administration with miglustat.

Carcinogenicity

No long-term animal studies have been performed to evaluate the carcinogenic potential of cipaglucosidase alfa with or without co-administration with miglustat.

Reproductive and Developmental Toxicology

In a segment I fertility and early embryonic development study, female rats were administered 70, 150 or 400 mg/kg bw cipaglucosidase alfa by intravenous injection, 60 mg/kg bw oral miglustat, or 400 mg/kg bw cipaglucosidase alfa in combination with miglustat (60 mg/kg bw) every other day for 14 days prior to mating with un-dosed males and continuing through gestation day 7 (GD 7). Male rats

were administered 70, 150 or 400 mg/kg bw cipaglucosidase alfa by intravenous injection, 60 mg/kg bw oral miglustat, or 400 mg/kg bw cipaglucosidase alfa in combination with miglustat (60 mg/kg bw) every other day for 6 weeks beginning 28 days prior to mating with un-dosed females. Fertility indices were not affected in males or females. Pre-implantation loss was observed in the female fertility component of the study in both miglustat alone and the combination treatment group. Whether this pre-implantation loss in female rats would be reversible if treatment were discontinued prior to cohabitation is unknown. Pre-implantation loss in naïve females mated with treated males was observed in the combination group. However, lower pre-implantation loss was observed in naïve females mated with treated males during the 2-week recovery period. There was no effect of cipaglucosidase alfa in combination with miglustat therapy or cipaglucosidase alfa alone on spermatogenesis. A NOAEL for developmental toxicity was not identified for the combination dose. Observed pre-implantation loss occurred at the LOAEL of 400 mg/kg bw cipaglucosidase with 60 mg/kg bw miglustat with systemic exposure approximately 27-fold (cipaglucosidase alfa AUC) and 4-fold (miglustat AUC) that of human exposure at the maximum recommended human dose (MRHD) of 20 mg/kg bw cipaglucosidase alfa with 260 mg miglustat for females rats on GD 7, respectively, based on $AUC_{0\text{-}24h}$ of 38050 µg·h/mL for cipaglucosidase alfa and 87600 ng·h/mL for miglustat with the combined dose.

In a segment II embryo-fetal development study, pregnant rats were administered 70, 150 or 400 mg/kg bw cipaglucosidase alfa by intravenous injection, 60 mg/kg bw oral miglustat, or 400 mg/kg bw cipaglucosidase in combination with miglustat (60 mg/kg bw) every other day during gestation from GD 6 to GD 18. No adverse findings were observed in pregnant rats or their offspring when cipaglucosidase was administered alone or in combination with miglustat. Systemic exposure at the NOAEL of 400 mg/kg bw cipaglucosidase with 60 mg/kg bw miglustat is 20-fold and 4-fold that of humans at the MRHD (20 mg/kg bw cipaglucosidase alfa with 260 mg miglustat), based on $AUC_{0\text{-}24h}$ of 28850 µg·h/mL and 84300 ng·h/mL, for cipaglucosidase alfa and miglustat, respectively, with the combined dose.

In an embryo-fetal development study in rabbits, pregnant animals were administered 30, 70 or 175 mg/kg bw cipaglucosidase alfa by intravenous injection, 25 mg/kg bw oral miglustat, or 150 mg/kg bw cipaglucosidase in combination with miglustat (25 mg/kg bw) every other day during gestation from GD 7 to GD 19. Adverse effects occurred at the LOAEL combination dose (175 mg/kg cipaglucosidase alfa with 25 mg/kg oral miglustat) including decreased maternal food consumption, body weight gains, and an increase in cardiovascular malformations (e.g., atretic pulmonary trunk, ventricular septum defect, and dilated aortic arch) in offspring. A NOAEL could not be established for the combination group since only one combination dose was tested. These findings occurred at 16-fold and 3-fold the exposure at the MRHD of cipaglucosidase alfa and miglustat (20 mg/kg bw cipaglucosidase with 260 mg miglustat), respectively, based on $AUC_{0\text{-}24h}$ of 22550 µg·h/mL and 66100 ng·h/mL, for cipaglucosidase alfa and miglustat, respectively, with the combined dose. It is not possible to exclude that the embryo-fetal adverse effects observed in the rabbits could have occurred following a single exposure to the combination.

In a segment III pre- and post-natal development study in rats, pregnant animals were administered 70, 150 or 400 mg/kg bw cipaglucosidase alfa by intravenous injection, 60 mg/kg bw oral miglustat, or 400 mg/kg bw cipaglucosidase in combination with miglustat (60 mg/kg bw) every other day during gestation from GD 6 to GD 20 and from lactation day (LD) 1 to LD 19. Increased maternal and pup mortality was observed at the combination dose. A NOAEL could not be established for the combination group since only one combination dose was tested. Evaluation of milk in rats from the combination treatment group on LD 13 showed secretion of miglustat and excretion of cipaglucosidase alfa in rat milk. Milk to plasma ratios were 1.72 for miglustat and 0.038 for cipaglucosidase alfa.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]POMBILITI®

cipaglucosidase alfa for injection, lyophilized powder

This patient medication information is written for the person who will be taking **POMBILITI**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This patient medication information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **POMBILITI**, talk to a healthcare professional.

If you are eligible for home infusion of **POMBILITI**, you will receive an Infusion Diary with important information about possible risks and what to do if you have a reaction during your infusion. It also includes emergency contact details. Keep this diary easily accessible during your infusion. You can get extra copies if needed by contacting the healthcare professional.

Serious Warnings and Precautions

Hypersensitivity Reactions Including Anaphylaxis

- If you are treated with POMBILITI, you may experience a life-threatening hypersensitivity reactions, including anaphylaxis. Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available during POMBILITI administration. If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, infusion should be immediately paused, appropriate medical treatment should be initiated, and the benefits and risks of re-administration of POMBILITI should be considered.

Infusion-Associated Reactions (IARs)

- If you are treated with POMBILITI, you may experience severe IARs. If severe IARs occur, infusion should be immediately paused, appropriate medical treatment should be initiated, and the benefits and risks of re-administration of POMBILITI should be considered following severe IARs.

Risk of Acute Cardiorespiratory Failure in Susceptible Patients

- Individuals with acute underlying respiratory illness or compromised cardiac and/or respiratory function may be at risk of serious exacerbation of their cardiac or respiratory compromise due to fluid volume overload during POMBILITI infusion. Appropriate medical support and monitoring measures should be readily available during POMBILITI infusion.

What POMBILITI is used for:

- POMBILITI is a type of 'enzyme-replacement therapy' (ERT) that is used in combination with OPFOLDA (65 mg miglustat capsules) for the treatment of late--onset Pompe disease (LOPD) in adults weighing 40 kg or more.
- POMBILITI is always used with another medicine called 65 mg miglustat capsules. It is very important that you also read the Patient Medication Information of OPFOLDA (65 mg miglustat capsule).

How POMBILITI works:

People with Pompe disease have low levels of the enzyme acid alpha-glucosidase (GAA). This enzyme helps control levels of glycogen in the body.

In Pompe disease, high levels of glycogen build up in the muscles of the body. This keeps muscles, such as the muscles that help you walk, the muscles under the lungs that help you breathe, and the heart muscle, from working properly.

POMBILITI contains an artificial enzyme called cipaglucosidase alfa; it can replace the natural enzyme which is lacking in Pompe disease.

The ingredients in POMBILITI are:

Medicinal ingredients: cipaglucosidase alfa

Non-medicinal ingredients: citric acid monohydrate, mannitol, polysorbate 80, sodium citrate dihydrate

POMBILITI comes in the following dosage forms:

Lyophilized powder, 105 mg/vial

Do not use POMBILITI if:

- You have ever had life-threatening hypersensitivity or infusion-related reactions (e.g., a severe allergic reaction and severe skin reactions) to:
  - cipaglucosidase alfa
  - miglustat
  - any of the other ingredients of this medicine or its container
- A previous infusion had to be stopped and could not be restarted due to life-threatening hypersensitivity reactions or infusion-related reactions
- You are pregnant or planning to become pregnant.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take POMBILITI. Talk about any health conditions or problems you may have, including if you:

- have allergic reactions, including anaphylaxis (a severe allergic reaction) (see "Possible side effects from using POMBILITI" section for symptoms of life-threatening reactions).
- have an infusion-associated reaction while you are receiving the medicine or in the few hours afterwards (see "Possible side effects from using POMBILITI" section for symptoms of life-threatening reactions).
- have a history of heart or lung disease. These conditions may worsen during or immediately after your infusion with POMBILITI. Tell your healthcare professional or nurse immediately if you are experiencing shortness of breath, cough, rapid or irregular heartbeat, or any other effects from these conditions.
- if you have swelling in your legs or widespread swelling of your body, severe skin rash, or frothy urine when passing water. Your healthcare professional will decide if your POMBILITI infusion should stop, and they will give you appropriate medical treatment. Your healthcare professional will also decide if you can continue receiving POMBILITI.
- have kidney problems

Other warnings you should know about:

- **Pre-treatment medications**

  Your healthcare professional may give you other medicines before you have POMBILITI. These medicines include:

  - antihistamines and corticosteroids to prevent or help reduce infusion-related reactions.
  - antipyretics to reduce fever.

- **Female patients**

  Pregnancy and birth control

  - There is no experience with the use of POMBILITI in combination with 65 mg miglustat capsules during pregnancy.
  - You must not receive POMBILITI and/or take 65 mg miglustat capsules if you are pregnant. There may be risks to the unborn baby.
  - If you are able to become pregnant:
    - your healthcare professional will make sure you are not pregnant before you start taking POMBILITI in combination with 65 mg miglustat capsules.
    - you must use reliable birth control methods during use, and for 4 weeks after stopping both medicines.
    - tell your healthcare professional immediately if you get pregnant, think that you may be pregnant, or if you are planning to become pregnant.

  Breast-feeding

  - If you are breast-feeding, do NOT take POMBILITI in combination with 65 mg miglustat capsules. A decision will need to be made whether to stop treatment or to stop breast-feeding.
  - Talk to your healthcare professional about the best way to feed your baby during treatment.

- **Fertility – male and female patients**

  - Taking POMBILITI in combination with 65 mg miglustat capsules may affect your ability to have children. Talk to your healthcare professional if this is a concern for you.

- **Driving and using machines**

  - Taking POMBILITI in combination with 65 mg miglustat capsules can cause dizziness, low blood pressure and drowsiness. You should use caution when driving or operating potentially dangerous machinery after receiving treatment or other pre-treatment medicines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take POMBILITI:

POMBILITI will be given to you under the supervision of a healthcare professional. It is given through a drip into a vein. This is called an intravenous infusion.

You may be eligible for treatment at home based on evaluation by your healthcare professional. Your healthcare professional will decide upon evaluation if it is safe for you to have home infusion of

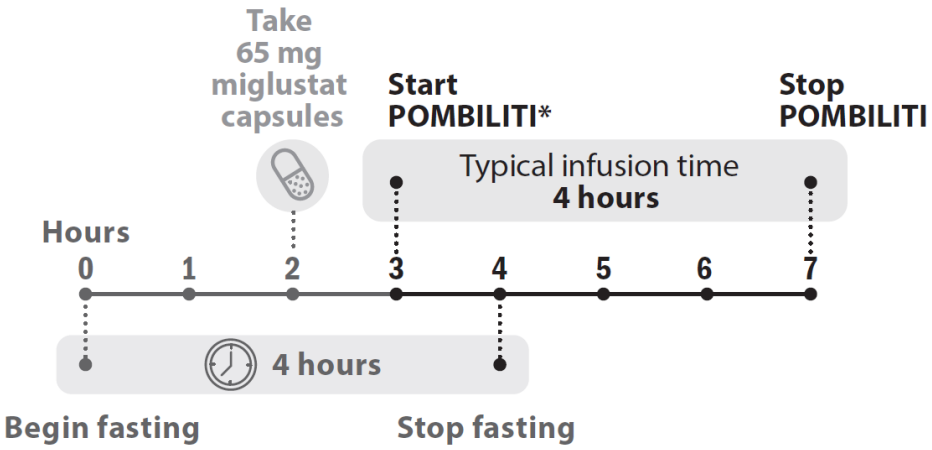
POMBILITI. If you get any side effects during an infusion of POMBILITI, your home infusion staff member may stop the infusion and start appropriate medical treatment.

POMBILITI should be used in conjunction with 65 mg miglustat capsules. You can only use miglustat 65 mg capsules with POMBILITI. Do **NOT** use miglustat 100 mg capsules (different product). Follow your healthcare professional's instructions and read the Patient Medication Information of OPFOLDA (65 mg miglustat capsule) for their recommended dose.

Usual dose:

- The amount of medicine that you will be given is based on your weight. The recommended dose of POMBILITI is 20 mg for each kg of body weight once every other week as an intravenous infusion.
- 65 mg miglustat capsules are taken on the same day as POMBILITI. Refer to the Patient Medication Information of OPFOLDA (65 mg miglustat capsule) for information on how to take miglustat.
  - The POMBILITI infusion should start 1 hour after taking 65 mg miglustat capsules.
- In the event of a delay, the start of infusion should not exceed 3 hours from taking 65 mg miglustat capsules.
- The infusion of POMBILITI lasts approximately 4 hours.

Figure 1 - Dose timeline



* You should take 65 mg miglustat capsules 1 hour before receiving POMBILITI infusion. In the event of POMBILITI infusion delay, your healthcare professional will ensure that infusion is started within 3 hours of taking 65 miglustat capsules.

Switching from another enzyme replacement therapy (ERT):

If you are currently being treated with another ERT:

- Your healthcare professional will tell you when to stop the other ERT before starting POMBILITI.
- Tell your healthcare professional when you have completed your last dose.

Overdose:

There is no experience with overdose of POMBILITI and/or 65 mg miglustat capsules.

If you think you, or a person you are caring for, have taken too much POMBILITI, contact a healthcare professional, hospital emergency department, regional poison control centre immediately or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669), even if there are no signs or symptoms.

Missed Dose:

Forgotten dose:

If you miss a dose of 65 mg miglustat capsules, please speak to your healthcare professional and do not start your POMBILITI infusion. You will need to re-start the treatment of 65 mg miglustat capsules in combination with POMBILITI as soon as possible.

Infusion delays:

If you have missed an infusion and it has been more than 3 hours since you have taken 65 mg miglustat capsules, please contact your healthcare professional as soon as possible to reschedule your appointment. Your next appointment should be scheduled at least 24 hours after 65 mg miglustat capsules were last taken.

Possible side effects from using POMBILITI:

These are not all the possible side effects you may have when taking POMBILITI. If you experience any side effects not listed here, tell your healthcare professional.

POMBILITI is used with 65 mg miglustat capsules, and side effects can occur with either of these medicines. Side effects were mainly seen while patients were being infused with POMBILITI (infusion-related effects) or shortly after. You must tell your healthcare professional immediately if you get an infusion-associated reaction or an allergic reaction. Some of these reactions may become serious and life-threatening. Your healthcare professional may give you medicines before your infusion to prevent these reactions.

If you get any side effects during an infusion of POMBILITI, the infusion may be stopped, and appropriate medical treatment may be started.

The most significant infusion reactions included allergic reactions and allergic shock to POMBILITI.

Cardiorespiratory Risk

If you have underlying compromised cardiac or respiratory function (including respiratory illness), you may be at increased risk of acute cardiorespiratory failure from volume overload during POMBILITI infusion. Seek medical care if you experience acute onset of dizziness, shortness of breath, sweating, wheezing, leg swelling.

- Headache
- Involuntary shaking of one or more parts of the body
- Feeling sleepy
- Altered sense of taste
- Sensation like numbness, tingling, pins, and needles
- Rapid heartbeat
- Loose, runny stools

- Nausea
- Stomach pain
- Passing gas or wind
- Bloating
- Vomiting
- Trouble passing stools
- Increased sweating
- Muscle cramps, muscle pain, muscle weakness
- Pain in joints
- Feeling tired all the time
- Feeling uncomfortable in chest
- Swelling or pain in the body area where needle was inserted
- Pain
- Swelling in the hands, feet, ankles, legs
- Rise in blood pressure
- Stomach discomfort
- Cannot hold or maintain balance
- Burning sensation
- Pain in one or both sides of the head, throbbing pain, aura, eye pain, sensitivity to light (migraine)
- Unusual paleness of the skin
- Breathing difficult and triggers coughing, and shortness of breath (asthma)
- Throat discomfort
- Indigestion
- Sore or irritated throat
- Painful and abnormal contractions of the throat
- Mouth pain or discomfort (oral pain and oral discomfort)
- Swollen tongue
- Skin discoloration
- Swelling of the skin
- Pain in the area between the hip and rib
- Muscle fatigue
- Increased rigidity of muscles
- Constant feeling of being tired
- Pain in the cheek, gums, lips, chin
- Feeling jittery
- Feeling of uneasiness, overall feeling of being sluggish
- Pain in chest
- Swelling face
- Changes in body temperature
- Decrease in a type of white blood cell - shown in tests
- Scratch or damage to the skin

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Common			
Infusion related reactions including **anaphylaxis** (severe allergic reaction): difficulty swallowing or breathing, fever, chills, cough, flushing, dizziness, wheezing, feeling sick to your stomach and throwing up, feeling close to fainting, low blood pressure, hives or rash, swelling of the face, lips, tongue or throat.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep out of reach and sight of children.

Do not use this medicine after the expiry date which is stated on the bottle and carton after the letters "EXP". The expiry date refers to the last date of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines that you no longer use.

Unopened vials:

Do not freeze. Store under refrigeration (2°C to 8°C). Store in original container to protect from light.

After reconstitution and dilution:

After dilution, an immediate use is recommended.

The reconstituted product can be stored for up to 24 hours when refrigerated at 2°C to 8°C. Storage at room temperature is not recommended.

The diluted product can be stored for up to 24 hours when refrigerated at 2°C to 8°C, followed by up to 6 hours when stored at room temperature at 20°C to 25°C.

If you want more information about POMBILITI:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada Drug Product Database website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html, the manufacturer's website: https://www.amicustherapeutics.ca, or by calling 1-833-810-5008.

This leaflet was prepared by:

Amicus Therapeutics Canada Inc.
100 King Street West, Suite 1600
1 First Canadian Place
Toronto ON M5X 1G5
Canada

Date of Authorization: 2025-04-15