▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – POMBILITI® (CIPAGLUCOSIDASE ALFA)

1 NAME OF THE MEDICINE

POMBILITI cipaglucosidase alfa 105 mg/7 mL powder for injection vial.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 105 mg of cipaglucosidase alfa.

After reconstitution of each vial (see Section 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL), the concentrated solution contains 15 mg of cipaglucosidase alfa* per mL.

*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 catalysing the hydrolysis of α-1,4- and α-1,6-glycosidic linkages of lysosomal glycogen.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Powder for injection

White to slightly yellowish lyophilised powder

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

POMBILITI (cipaglucosidase alfa) is a long-term enzyme replacement therapy used in combination with the enzyme stabiliser miglustat for the treatment of adults with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency).

4.2 DOSE AND METHOD OF ADMINISTRATION

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

POMBILITI must be used in combination with miglustat 65 mg capsules. The prescribing information for miglustat 65 mg capsules should be consulted before prescribing POMBILITI.

The recommended dose of POMBILITI is 20 mg/kg body weight administered every other week as an intravenous solution for IV administration.

Method of administration

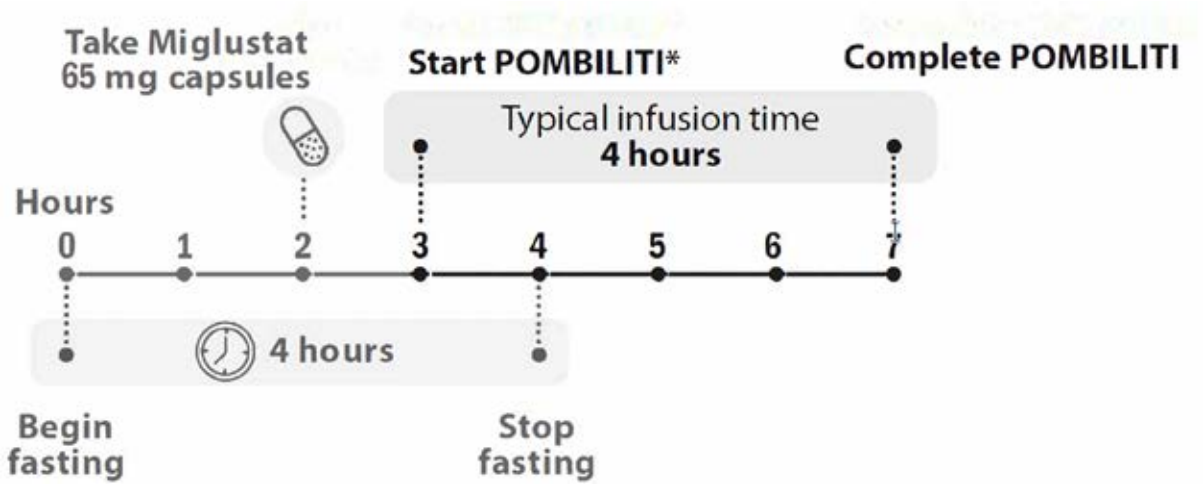
POMBILITI is to be administered by intravenous infusion.

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 body weight range is ≥ 40 kg. 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 after the patient's tolerance to the infusion rate is established, 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 IARs. In the event of severe allergic reaction or anaphylaxis, immediately stop the infusion, and appropriate medical treatment should be initiated, (see Sections 4.3 CONTRAINDICATIONS and 4.4 SPECIAL WARNING AND PRECAUTIONS).

Infusion can be administered in all sites of patient care including at home, in-clinic, and in-hospital after comprehensive evaluation of infusion-associated reactions (IARs) risks under the supervision of a healthcare professional (see Sections 4.3 CONTRAINDICATIONS and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Product is for single use in one patient only and contains no antimicrobial preservative. Discard any residue.

Figure 1: Dose Timeline



* The POMBILITI infusion should start 1 hour after taking miglustat 65 mg capsules. In the event of infusion delay, the start of infusion should not exceed 3 hours from taking miglustat 65 mg capsules. See below "Missed Dose".

Home infusion

Infusion of POMBILITI at home may be considered for patients after evaluation and upon recommendation by the treating physician (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). The treating physician should be consulted if the patient experiences significant infusion reactions or if changes to recommended dose and/or infusion rate are required.

Preparation before the infusion

Use aseptic technique.

Each vial of POMBILITI is for single-dose-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.

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 7.0 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 injections 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

  Note: Choose a bag size based on the patient's body weight.
- A needle of **18 gauge or lesser diameter**

Activities before reconstitution

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

Reconstituting the lyophilised powder

1. Reconstitute each vial by slowly adding 7.2 mL sterile water for injections dropwise down the inside of the vial rather than directly onto the lyophilised powder. Avoid forceful impact of sterile water for injections on the lyophilised powder and avoid foaming.
2. 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.
3. Perform an inspection of the reconstituted vials for particulate matter and discolouration. The reconstituted volume appears as a colourless 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 discoloured, do not use.

   Each reconstituted vial has a **concentration of 15 mg/mL** with an extractable volume of 7.0 mL.
4. Repeat above steps for the number of vials needed for dilution.

Dilution and preparation of the infusion bag

1. 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 POMBILITI needed for the bag.

2. Slowly withdraw 7 mL of the reconstituted solution from the vials, including less than the 7.0 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 POMBILITI solution 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. Do not shake or excessively agitate the bag for infusion. After dilution, the solution will have a final concentration of 0.5 to 4 mg/mL of POMBILITI. 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 POMBILITI solution required for the patient's dose.

The infusion solution should be administered as close to after dilution preparation as possible at room temperature (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Preparing for administration

If it is not possible to start the infusion following dilution, the reconstituted and diluted solution is stable for up to 30 hours refrigerated at 2°C to 8°C. Storage at room temperature is not recommended, refer to the in-use stability storage conditions. Do not freeze or shake.

The normal saline bag for infusion containing POMBILITI 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 IV-line blocks during infusion, change the filter.

Other medicines should not be infused in the same IV line as the diluted POMBILITI solution.

<u>Missed dose</u>

If the POMBILITI infusion cannot be started within 3 hours of oral administration of miglustat 65 mg capsules, reschedule treatment of POMBILITI and miglustat 65 mg capsules at least 24 hours after taking miglustat 65 mg capsules. If POMBILITI and miglustat 65 mg 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.

Patient response to treatment should be routinely evaluated based on a comprehensive evaluation of all clinical manifestations of the disease. In case of an insufficient response or intolerable safety risks, discontinuation of POMBILITI in combination with miglustat 65 mg

capsules treatment should be considered, see Section 4.4 SPECIAL WARNING AND PRECAUTIONS. Both medicinal products should either be continued or discontinued.

Switching patients from another enzyme replacement therapy (ERT)

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

Patients who have switched from another ERT to POMBILITI in combination with miglustat 65 mg capsules 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 (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Premedication and/or treatment during infusion with corticosteroids, antihistamines, and antipyretics may be administered to assist with signs and symptoms related to IARs (see Sections 4.3 CONTRAINDICATIONS and 4.4 SPECIAL WARNING AND PRECAUTIONS).

Dose adjustment

Hepatic impairment

The safety and efficacy of POMBILITI in combination with miglustat 65 mg capsules therapy have not been evaluated in patients with hepatic impairment. No dose adjustment can be recommended for hepatically impaired patients.

Renal impairment

The safety and efficacy of POMBILITI in combination with miglustat 65 mg capsules therapy have not been evaluated in patients with renal impairment. When administering every other week, increased plasma miglustat exposure as a result of moderate or severe renal impairment is not expected to appreciably impact cipaglucosidase alfa exposures and is not anticipated to affect efficacy and safety of cipaglucosidase alfa in a clinically meaningful manner. No dose adjustment is required in patients with renal impairment.

Elderly

There is limited experience with the use of POMBILITI in combination with OPFOLDA therapy in patients above the age of 65 years. There is no dose adjustment required in patients ≥ 65 years of age (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Paediatric population

The safety and effectiveness of POMBILITI in combination with miglustat 65 mg capsules therapy have not been established in paediatric patients.

4.3 CONTRAINDICATIONS

- Patients with a history of life-threatening infusion-associated reactions (IARs) (eg, anaphylaxis and severe cutaneous reactions) to the active substance, or to any of the excipients listed in Section 6.1 LIST OF EXCIPIENTS, when rechallenge was unsuccessful (see Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.8 ADVERSE EFFECTS [UNDESIRABLE EFFECTS]).
- Patients with a contraindication to miglustat.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Anaphylaxis and infusion-associated reactions

Serious anaphylaxis and IARs have occurred in some patients during infusion and following infusion with POMBILITI (see Section 4.8 ADVERSE EFFECTS [UNDESIRABLE EFFECTS]). Premedication with oral antihistamine, antipyretics, and/or corticosteroids may be administered to assist with signs and symptoms related to IARs 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 IARs. Mild to moderate and transient IARs may be adequately managed by slowing the infusion rate or interrupting the infusion; medical treatment or discontinuation of POMBILITI may not be required.

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.

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 during infusions. Appropriate medical support and monitoring measures should be readily available during POMBILITI infusion.

Immune complex-related reactions

Immune complex-related reactions have been reported with other ERTs 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 OPFOLDA therapy. 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 reconsidered for each individual patient.

Use in hepatic impairment

The safety and efficacy of POMBILITI in combination with OPFOLDA therapy have not been evaluated in patients with hepatic impairment.

Use in renal impairment

The safety and efficacy of POMBILITI in combination with OPFOLDA therapy have not been evaluated in patients with renal impairment. No dose adjustment is required in patients with renal impairment (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in the elderly

There is limited experience with the use of POMBILITI in combination with OPFOLDA therapy in patients above the age of 65 years old. There is no dose adjustment required in patients ≥ 65 years of age (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Paediatric use

The safety and effectiveness of POMBILITI in combination with OPFOLDA therapy have not been established in paediatric patients.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No drug-drug interaction studies have been conducted using cipaglucosidase alfa or cipaglucosidase alfa in combination with miglustat.

4.6 FERTILITY, PREGNANCY AND LACTATION

Contraception in females

Reliable contraceptive measures must be used by women of childbearing potential during treatment with POMBILITI in combination with OPFOLDA, and for 4 weeks after the last dose (see Effects on fertility). The medicinal product is not recommended in women of childbearing potential not using reliable contraception.

Effects on fertility

There are no clinical data on the effects of IV cipaglucosidase alfa (20 mg/kg) in combination with miglustat on fertility.

In a fertility study in male rats, there was no effect of IV cipaglucosidase alfa (400 mg/kg) in combination with miglustat (60 mg/kg) or cipaglucosidase alfa alone (400 mg/kg) on spermatogenesis.

In a fertility and early embryonic development study in rats treated with oral miglustat alone (60 mg/kg) and with the combination (cipaglucosidase alfa 400 mg/kg IV with oral miglustat 60 mg/kg) every other day for 14 days prior to mating and continuing through gestation day 7 (GD 7), pre-implantation loss was observed in the female fertility component of the study in both miglustat alone and the combination treatment group and was considered miglustat related. Whether this pre-implantation loss in female rats would be reversible if treatment were discontinued prior to cohabitation is unknown.

Use in pregnancy

Category D

There are no clinical data for the use of POMBILITI in combination with OPFOLDA in pregnant women. Animal studies with miglustat alone as well as with cipaglucosidase alfa in combination with miglustat have shown reproductive toxicity. POMBILITI in combination with OPFOLDA therapy is not recommended during pregnancy.

In an embryofetal development study in rats dosed with cipaglucosidase alfa (up to 400 mg/kg IV) and/or oral miglustat (60 mg/kg), no adverse findings were observed in pregnant rats or their offspring at 20-fold and 4-fold the exposure at the maximum recommended human dose (MRHD) of cipaglucosidase alfa and miglustat, respectively.

In an embryofetal development study in rabbits, maternal effects including decreased food consumption and body weight gains were evident for the combination group (cipaglucosidase alfa 175 mg/kg IV with oral miglustat 25 mg/kg). Additionally, the results included an increase in cardiovascular malformations (aortic pulmonary trunk, ventricular septum defect, and dilated aortic arch) at 16-fold and 3-fold the exposure at the MRHD of cipaglucosidase alfa and miglustat, respectively. A NOAEL could not be established for the combination group since only one combination dose was tested.

Use in lactation

It is not known if cipaglucosidase alfa and miglustat are secreted in human breast milk. Available pharmacodynamic/toxicological data in animals have shown secretion of miglustat and excretion of cipaglucosidase alfa in milk. A risk to newborns/infants cannot be excluded. Patients should be advised to discontinue breastfeeding while on treatment with POMBILITI in combination with OPFOLDA.

In a pre-and post-natal development study in rats, increased maternal and pup mortality was observed following treatment with the combination of cipaglucosidase alfa and miglustat at doses of 400 mg/kg for cipaglucosidase alfa and 60 mg/kg miglustat every second day (20-fold and 4.1-fold the exposure for cipaglucosidase alfa and miglustat at the MRHD, respectively). Decreased pup weight was also observed following treatment with the combination at this dose. Evaluation of milk in rats from the combination treatment group showed secretion of miglustat and excretion of cipaglucosidase alfa in rat milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

POMBILITI may have minor influence on the ability to drive and to use machines since dizziness, hypotension, and somnolence have been reported as adverse reactions. Caution is required when driving or using any tools or machines after receiving POMBILITI.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The pooled safety analysis from 3 clinical trials included 151 adult patients with late-onset Pompe disease (LOPD) treated with POMBILITI in combination with OPFOLDA including:

- 85 patients in the randomised, double-blind, active-controlled trial in adults (the PROPEL trial; see Section 5.1 PHARMACODYNAMIC PROPERTIES),
- 37 patients in the open-label extension trial where patients switched from an approved alglucosidase alfa product in the PROPEL trial (see Section 5.1 PHARMACODYNAMIC PROPERTIES) to POMBILITI in combination with OPFOLDA,
- 29 patients in an open-label trial.

The most common reported adverse reactions (≥ 5%) reported in POMBILITI-OPFOLDA 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%).

Tabulated list of adverse reactions

The assessment of adverse reactions was informed by subjects treated with POMBILITI in combination with OPFOLDA therapy across 3 clinical trials. The total mean duration of exposure was 28 months.

The corresponding frequency category for each treatment-related adverse event is based on the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), and not known (cannot be estimated from available data). Adverse reactions from the clinical trials are listed by MedDRA system organ class in Table 1.

Table 1: Summary of Adverse Reactions from Three Clinical Trials

System Organ Class (SOC)	Frequency	Adverse Reaction (Preferred Term)
Immune system disorders	Common	Anaphylactic reaction‡[6]
	Uncommon	Hypersensitivity
Nervous system disorders	Very Common	Headache
	Common	Dizziness*, tremor, somnolence*, dysgeusia, paraesthesia
	Uncommon	Balance disorder, burning sensation*, migraine‡[4], presyncope*
Cardiac disorders	Common	Tachycardia‡[7]
Vascular disorders	Common	Flushing*, hypotension
	Uncommon	Pallor
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea, cough*
	Uncommon	Asthma, oropharyngeal discomfort*, pharyngeal oedema*, wheezing*
Gastrointestinal disorders	Common	Diarrhoea, nausea, abdominal pain‡[1], vomiting, flatulence, abdominal distension, constipation†
	Uncommon	Abdominal discomfort†, dyspepsia*, oesophageal pain*, oesophageal spasm, oral discomfort*, oral pain, swollen tongue*
Skin and subcutaneous tissue disorders	Common	Urticaria‡[3], rash‡[2], pruritus, hyperhidrosis
	Uncommon	Skin discolouration, skin oedema*
Musculoskeletal and connective tissue disorders	Common	Muscle spasms, myalgia, arthralgia, muscular weakness
	Uncommon	Flank pain, muscle fatigue, musculoskeletal stiffness
General disorders and administration site conditions	Common	Fatigue, pyrexia, chills, chest discomfort*, infusion site swelling*, pain*, peripheral swelling
	Uncommon	Asthenia, facial pain, feeling jittery†, infusion site pain*, malaise*, non-cardiac chest pain, swelling face*
Investigations	Common	Blood pressure increased‡[5]
	Uncommon	Body temperature fluctuation*, lymphocyte count decreased, platelet count decreased†
Injury, poisoning and procedural complications	Uncommon	Skin abrasion*

* Related to POMBILITI
† Related to OPFOLDA
‡ 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, rash macular, and infusion site rash are grouped under rash.
[3] Urticaria, mechanical urticaria, and urticaria rash are grouped under urticaria.
[4] Migraine and migraine with aura are grouped under migraine.
[5] Hypertension and blood pressure increased are grouped under blood pressure increased.
[6] Anaphylaxis and anaphylactic reaction are grouped under anaphylactic reaction. Anaphylactoid reaction is manually coded to anaphylaxis.
[7] Tachycardia and sinus tachycardia are grouped under tachycardia.

Tabulated list of treatment-emergent adverse events from PROPEL trial

The most commonly reported treatment-emergent adverse events (TEAEs) (≥ 10%) from either treatment group in controlled trial (PROPEL) are shown in Table 2. The most frequently reported TEAEs in the POMBILITI in combination with OPFOLDA group were fall, headache, nasopharyngitis and myalgia. The most frequently reported TEAEs in the alglucosidase alfa/placebo group were fall, headache, nausea, and back pain.

Table 2 shows adverse events with an incidence of at least 10% in either treatment group from the controlled trial (PROPEL).

Table 2: Adverse Events with an Incidence of at Least 10% of Subjects by Preferred Term (PROPEL trial)

Preferred Term - n (%)	POMBILITI in combination with OPFOLDA (N = 85)	Alglucosidase Alfa/Placebo (N = 38)
Subjects with any TEAE	81 (95.3)	37 (97.4)
Fall	25 (29.4)	15 (39.5)
Headache	20 (23.5)	9 (23.7)
Nasopharyngitis	19 (22.4)	3 (7.9)
Myalgia	14 (16.5)	5 (13.2)
Diarrhoea	11 (12.9)	4 (10.5)
Nausea	10 (11.8)	8 (21.1)
Arthralgia	13 (15.3)	5 (13.2)
Back pain	9 (10.6)	7 (18.4)
Urinary tract infection	12 (14.1)	2 (5.3)
Fatigue	8 (9.4)	5 (13.2)
Pain in extremity	11 (12.9)	2 (5.3)
Musculoskeletal pain	10 (11.8)	2 (5.3)
Oropharyngeal pain	10 (11.8)	2 (5.3)
N = total number of subjects; n = number of subjects in category indicated; TEAE = emergent adverse event		

Description of selected adverse reactions

Infusion associated reactions (IARs)

The following IARs were reported in at least 2 subjects in the PROPEL trial during the POMBILITI infusion or within 2 hours after completion of the infusion: abdominal distension, chills, pyrexia, dizziness, dysgeusia, dyspnoea, pruritus, rash, and flushing. 0.7% of patients experienced a serious adverse reaction of anaphylaxis (characterised by generalised pruritus, dyspnoea, and hypotension) during the PROPEL trial receiving POMBILITI and OPFOLDA. 1.3% of patients receiving POMBILITI and OPFOLDA discontinued treatment due to IARs (anaphylaxis and chills). Most IARs were mild or moderate in severity and 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 OPFOLDA.

Immunogenicity

The observed incidence of antidrug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of antidrug antibodies (ADA) in the trials described below with the incidence of antidrug antibodies in other trials.

In the Phase 3 trial (PROPEL), the percent of ERT-naïve subjects with positive specific anti-rhGAA antibodies and detectable titres increased from 0% at baseline to 87.5% at the last trial visit; the percent of ERT-experienced subjects with positive specific anti-rhGAA antibodies and detectable titres remained stable for subjects treated with POMBILITI (83.1% at baseline to 74.1% at last trial visit).

The majority of ERT-experienced and ERT-naïve subjects treated with POMBILITI were positive post-treatment for neutralising antibodies (Nabs). The incidence of enzyme activity inhibition Nabs was similar between subjects treated with either POMBILITI or with alglucosidase alfa.

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 or with total anti-rhGAA antibodies.

Overall, there was no apparent association between immunogenicity and safety, pharmacokinetics, or pharmacodynamic effects; however, patients should be monitored for signs and symptoms of systemic immune complex-related reactions (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no experience with overdose of POMBILITI (see Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.8 ADVERSE EFFECTS [UNDESIRABLE EFFECTS]).

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other alimentary tract and metabolism products, enzymes. ATC Code: A16Ab23

Mechanism of action

Cipaglucosidase alfa is intended to replace the absent or impaired endogenous enzyme in people with Pompe disease (acid α-glucosidase [GAA] deficiency). Cipaglucosidase alfa is stabilised by miglustat minimising the loss of enzyme activity in the blood during infusion of this hydrolytic glycogen-specific enzyme with bisM6P 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 which are both required to yield the most mature and the most active form of the GAA enzyme. The enzyme activity reduces intramuscular glycogen and ameliorates tissue damage.

Clinical trials

A 52-week Phase 3 randomised, double-blind, active-controlled, international, multi-centre clinical trial was conducted in adult subjects (≥ 18 years) diagnosed with late-onset Pompe disease. Subjects were randomised 2:1 to receive 20 mg/kg POMBILITI in combination with 195 mg or 260 mg OPFOLDA based on body weight or 20 mg/kg alglucosidase alfa in combination with placebo every other week for 52 weeks. The efficacy population included a total of 122 subjects of which 95 subjects had received prior ERT with alglucosidase alfa (ERT-experienced) and 27 had never received ERT (ERT-naïve).

Demographics, baseline 6-Minute Walk Distance (6MWD), and sitting percent predicted Forced Vital Capacity (FVC) were 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 trial (mean of 7.4 years).

The primary efficacy endpoint was change in 6-minute walk distance (6MWD) from baseline to Week 52. The first key secondary endpoint was change in sitting percent predicted Forced Vital Capacity (FVC).

Motor function

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

All subjects (ERT-experienced and ERT-naïve) treated with POMBILITI in combination with OPFOLDA therapy walked on average 20.8 metres farther from baseline as compared to those treated with alglucosidase alfa-placebo who walked 7.2 metres farther from baseline, indicating a POMBILITI in combination with OPFOLDA treatment effect of 13.6 metres. Statistically significant superiority was not achieved (p = 0.07) (Table 3).

The ERT-experienced subjects treated with POMBILITI in combination with OPFOLDA therapy (n = 65) had a mean improvement in walk distance from baseline of 16.9 metres as compared to a mean of 0 metres for alglucosidase alfa in combination with placebo (n = 30), indicating a POMBILITI in combination with OPFOLDA treatment effect of 16.9 metres (p = 0.047).

The ERT-naïve subjects treated with POMBILITI in combination with OPFOLDA therapy (n = 20) had a mean improvement in walk distance from baseline of 33.4 metres as compared to 38.3 metres for alglucosidase alfa in combination with placebo (n = 75).

Table 3: Summary of 6MWD in All Subjects at 52 Weeks

6MWD (metres)	POMBILITI in combination with OPFOLDA	Alglucosidase alfa in combination with placebo
Baseline n Mean (SD) Median	 n = 85 357.9 (111.8) 359.5	 n = 37 351.0 (121.3) 365.5
Change from baseline at Week 52 n Mean (SD) (95% CI) Median	 n = 85 20.8 (42.8) (11.6, 30.0) 12.5	 n = 37 7.2 (40.3) (-6.2, 20.7) 1.4
Change to Week 52 Diff. of LS means (SE) (95% CI) 2-sided p value*	 13.7 (7.6) (-1.2, 28.5) p = 0.071	

* Statistical superiority was not achieved.
LS: least square; SD: standard deviation; SE: standard error; CI: confidence interval; Diff.: difference
Diff. in change to Week 52 data based on nonparametric randomisation-based ANCOVA analysis of the ITT-LOCF population excluding outlier.

Pulmonary function

Sitting percent predicted Forced Vital Capacity (FVC) at 52 weeks

All subjects (ERT-experienced and ERT-naïve) treated with POMBILITI in combination with OPFOLDA showed a mean change in FVC from baseline of -0.9% as compared with subjects treated with alglucosidase alfa-placebo of -4.0%, indicating a POMBILITI in combination with OPFOLDA treatment effect of 3.0% (Table 4).

The ERT-experienced subjects treated with POMBILITI in combination with OPFOLDA (n = 65) showed a mean change in FVC from baseline of +0.1% as compared with subjects treated with alglucosidase alfa-placebo of -4.0% (n = 30) indicating a POMBILITI in combination with OPFOLDA treatment effect of 4.1%.

The ERT-naïve subjects treated with POMBILITI in combination with OPFOLDA (n = 20) showed a mean change in FVC from baseline of -4.1% as compared with subjects treated with alglucosidase alfa-placebo (n = 7) of -3.6%, indicating similar rates of decline (-0.5% difference).

Table 4: Summary of Percent Predicted FVC in All Subjects at 52 Weeks

Sitting Percent Predicted FVC	POMBILITI in combination with OPFOLDA	Alglucosidase alfa-placebo
Baseline n Mean (SD) Median	 n = 85 70.7 (19.6) 70.0	 n = 37 69.7 (21.5) 71.0
Change from baseline at Week 52 n Mean (SD) (95% CI) Median	 n = 84 -0.9 (6.2) (-2.3, 0.4) -1.0	 n = 37 -4.0 (4.9) (-5.6, -2.3) -3.0
Change to Week 52 Diff. of LS means (SE) (95% CI)	2.7 (1.2) (0.4, 5.0)	

LS: least square; SD: standard deviation; SE: standard error; CI: confidence interval; Diff.: difference
Diff. in change to Week 52 data based on ANCOVA analysis of the ITT-LOCF population excluding outlier

Secondary endpoints

The observed effects for the secondary endpoints (eg, MMT, GSGC, CK, Hex 4, PROMIS-Physical Function, and PROMIS-Fatigue) supported the conclusions drawn from the 6MWD and sitting percent predicted FVC.

Subjects who were treated with 20 mg/kg POMBILITI in combination with the enzyme stabiliser OPFOLDA every other week showed a mean reduction of -22.4% in CK compared to a mean increase of +15.6% in the alglucosidase alfa and placebo treated subjects, and a mean reduction of -31.5% in Hex-4 compared to a mean increase of +11.0% in subjects who were treated with alglucosidase alfa and placebo after 52 weeks.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Cipaglucosidase alfa was evaluated with and without miglustat in 11 ambulatory ERT-experienced subjects with LOPD, reached peak concentrations at approximately the end of the 4-hour duration of IV infusion, and declined in a biphasic manner to 24 hours from the start of infusion.

Table 5: Pharmacokinetic Summary at Clinical Dose

PK Parameter	Cipaglucosidase alfa 20 mg/kg in combination with miglustat 260 mg	Cipaglucosidase alfa 20 mg/kg
C_{max} (mcg/mL)	345 (18.5)	325 (13.5)
$AUC_{0-\infty}$ (mcg*h/mL)	1812 (20.8)	1410 (15.9)

$AUC_{0-\infty}$ = area under the curve from time 0 to infinity; C_{max} = maximum observed plasma concentration

Distribution

The distribution (alpha) half-life increased by 47% following administration of the clinical dose regimen of both cipaglucosidase alfa and miglustat relative to 20 mg/kg cipaglucosidase alfa alone. The population PK model predicted cipaglucosidase alfa central compartment volume of distribution to be 3.24 L.

Metabolism

The metabolic pathway of cipaglucosidase alfa has not been characterised. As a glycoprotein, cipaglucosidase alfa is expected to be degraded to small peptides or amino acids via non-saturable catabolic pathways.

Excretion

Cipaglucosidase alfa is eliminated primarily in the liver by proteolytic hydrolysis. The mean terminal elimination half-life for cipaglucosidase alfa ranged from 1.6 to 2.6 hours.

Special populations

Gender, elderly, and race/ethnicity

Based on a pooled population pharmacokinetic analysis, gender and race did not have a clinically meaningful effects on POMBILITI in combination with OPFOLDA exposures. There is limited experience with the use of POMBILITI in combination with OPFOLDA therapy in patients above the age of 65 years old. There is no dose adjustment required in elderly patients.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Genotoxicity studies have not been conducted with cipaglucosidase alfa. As a high molecular weight protein, cipaglucosidase alfa is not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity

Carcinogenicity studies have not been conducted with cipaglucosidase alfa. As a recombinant glycoprotein, cipaglucosidase alfa is not expected to exhibit carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

citric acid monohydrate

mannitol

polysorbate 80

sodium citrate dihydrate

Refer to Section 2 QUALITATIVE AND QUANTITATIVE COMPOSITION.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Reconstituted medicinal product

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

Infusion Preparation*	**In-use Stability**	
	Refrigerated Storage (2°C to 8°C)	**Room Temperature Storage** (20°C to 25°C)
Once POMBILITI vial is reconstituted with sterile water for injections:	24 hours	Not recommended
Once reconstituted vial is diluted with sodium chloride 9 mg/mL (0.9%) solution for injection in the infusion bag:	24 hours	6 hours
* To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2-8°C for not more than 24 hours.		

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in original container or equivalent to protect from light.

Do not freeze. Store at 2°C to 8°C.

For storage conditions after reconstitution and dilution of the medicinal product, see Section 6.3 SHELF LIFE.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type

One 20 mL vial contains 105 mg of cipaglucosidase alfa. It is supplied in a neutral borosilicate clear glass vial sealed with a 20 mm chlorobutyl rubber stopper with an aluminium overseal with a dark grey flip-off cap.

Pack sizes

Packs containing 1, 10, and 25 vials.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

CAS number

2359727-71-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Amicus Therapeutics Pty Ltd
Level 10, 20 Martin Place
Sydney NSW 2000
Australia
Free call: 1300 264 287
Email: MedInfoAustralia@amicusrx.com

9 DATE OF FIRST APPROVAL

17 February 2025

10 DATE OF REVISION

Not Applicable

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
-	New