ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Pombiliti 105 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 105 mg of cipaglucosidase alfa.

After reconstitution of each vial (see section 6.6), the concentrated solution contains 15 mg of cipaglucosidase alfa* per mL.

*Human acid α-glucosidase with bis-phosphorylated N-glycans (bis-M6P) is produced in Chinese hamster ovary cells (CHO) by recombinant DNA technology.

Excipient with known effect

Each vial contains 10.5 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate)

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 Posology and method of administration

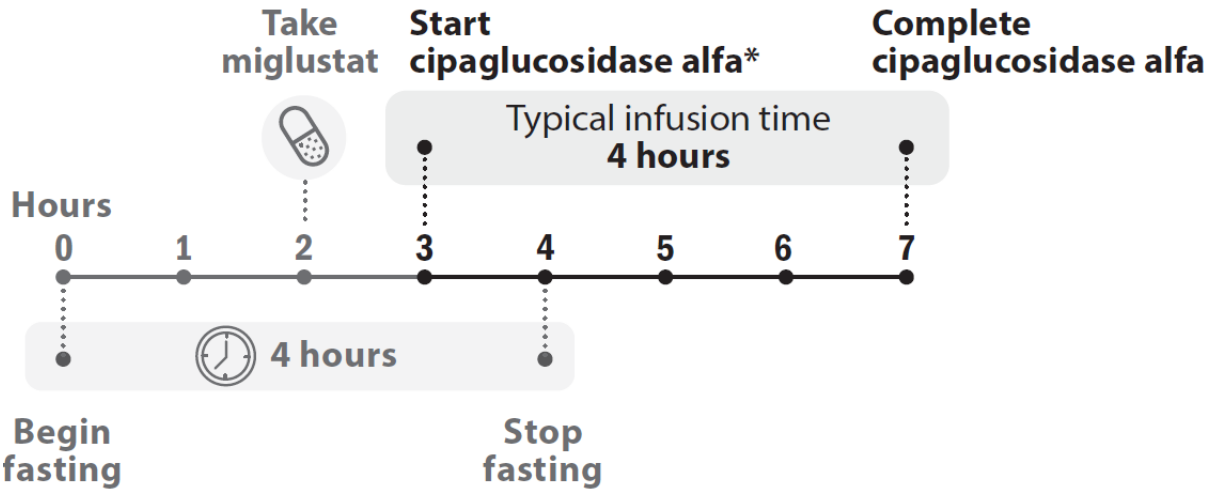
Treatment should be supervised by a physician experienced in the management of patients with Pompe disease or other inherited metabolic or neuromuscular diseases.

Cipaglucosidase alfa must be used in combination with miglustat 65 mg hard capsules. Because of this, the summary of product characteristics (SmPC) for miglustat 65 mg hard capsules should be consulted before taking cipaglucosidase alfa concerning number of capsules (based on body weight), dose time, and fasting.

Posology

The recommended dose of cipaglucosidase alfa is 20 mg/kg of body weight every other week. The Pombiliti infusion should start 1 hour after taking miglustat capsules. In the event of infusion delay, the start of infusion should not exceed 3 hours from taking miglustat.

Figure 1. Dose timeline



* The cipaglucosidase alfa infusion should start 1 hour after taking miglustat capsules. In the event of infusion delay, the start of infusion should not exceed 3 hours from taking miglustat.

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 cipaglucosidase alfa in combination with miglustat treatment should be considered, see section 4.4. 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 cipaglucosidase alfa in combination with miglustat therapy, the patient can be started with cipaglucosidase alfa-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 cipaglucosidase alfa in combination with miglustat therapy should be advised to continue with any premedications used with the previous ERT therapy to minimise infusion-associated reactions (IARs). Depending on tolerability, premedication may be modified, see section 4.4.

Missed dose
If the cipaglucosidase alfa infusion cannot be started within 3 hours of oral administration of miglustat, reschedule treatment of cipaglucosidase alfa and miglustat at least 24 hours after taking miglustat. If cipaglucosidase alfa and miglustat are both missed, treatment should occur as soon as possible.

Special populations

Elderly
There is limited experience with the use of cipaglucosidase alfa in combination with miglustat therapy in patients above the age of 65 years old. There is no dose adjustment required in elderly patients, see section 5.2.

Renal and hepatic impairment
The safety and efficacy of cipaglucosidase alfa in combination with miglustat therapy have not been evaluated in patients with renal and/or hepatic impairment. When administering every other week, increased plasma miglustat exposure as a result of moderate or severe renal or hepatic 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. The safety and efficacy of cipaglucosidase alfa in patients with hepatic impairment have not been evaluated and no specific dose regimen can be recommended for these patients.

Paediatric population
The safety and efficacy of cipaglucosidase alfa in combination with miglustat therapy in paediatric patients less than 18 years old have not yet been established. No data are available.

Method of administration

Cipaglucosidase alfa is to be administered by intravenous infusion.

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. An initial cipaglucosidase alfa infusion rate of 1 mg/kg/hr is recommended. This infusion rate may be gradually increased by 2 mg/kg/hr approximately every 30 minutes if there are no signs of IARs until a maximum infusion rate of 7 mg/kg/hr is reached. The rate of infusion should be guided by the patient's previous experience during infusion. The infusion rate may be slowed or temporarily stopped in the event of mild to moderate IARs. In the event of severe allergic, anaphylaxis, serious or severe IARs, the administration should immediately be discontinued, and appropriate medical treatment should be initiated, see sections 4.3 and 4.4.

Home infusion
Infusion of cipaglucosidase alfa 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. The decision to have a patient move to home infusion should be made after evaluation and upon recommendation by the treating physician. A patient's underlying co-morbidities and ability to adhere to the home infusion requirements need to be taken into account when evaluating the patient for eligibility to receive home infusion. 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 cipaglucosidase alfa infusions supervised by a physician with expertise in management of Pompe patients 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 healthcare professional. The healthcare professional should be always available during the home infusion and for a specified time after infusion, depending on patient's tolerance prior to starting home infusion.

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 section 4.4). 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 physician.

The reconstituted product prior to dilution appears as a clear to opalescent colourless to slightly yellow solution. For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Life-threatening hypersensitivity to the active substance, or to any of the excipients listed in section 6.1, when rechallenge was unsuccessful, see sections 4.4 and 4.8.

- Contraindication to miglustat.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Anaphylaxis and infusion-associated reactions

Serious anaphylaxis and IARs have occurred in some patients during infusion and following infusion with cipaglucosidase alfa, see section 4.8. 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 cipaglucosidase alfa 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 cipaglucosidase alfa 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 cipaglucosidase alfa 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 cipaglucosidase alfa with miglustat. If immune complex-related reactions occur, discontinuation of the administration of cipaglucosidase alfa should be considered and appropriate medical treatment should be initiated. The risks and benefits of re-

administering cipaglucosidase alfa following an immune complex-related reaction should be reconsidered for each individual patient.

Sodium

This medicinal product contains 10.5 mg sodium per vial. This is equivalent to 0.52% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed related to the use of cipaglucosidase alfa or with cipaglucosidase alfa in combination with miglustat. As cipaglucosidase alfa is a recombinant human protein, it is an unlikely candidate for cytochrome P450 or P-gP mediated interactions with other medicinal products.

4.6 Fertility, pregnancy and lactation

Contraception in females

Reliable contraceptive measures must be used by women of childbearing potential during treatment with cipaglucosidase alfa in combination with miglustat, and for 4 weeks after discontinuing treatment, see section 5.3. The medicinal product is not recommended in women of childbearing potential not using reliable contraception.

Pregnancy

There are no clinical data from the use of cipaglucosidase alfa in combination with miglustat in pregnant women. Cipaglucosidase alfa alone has not shown reproductive toxicity. Animal studies with miglustat alone as well as with cipaglucosidase alfa and miglustat have shown reproductive toxicity, see section 5.3. Cipaglucosidase alfa in combination with miglustat therapy is not recommended during pregnancy.

Breast-feeding

It is not known if cipaglucosidase alfa and miglustat are secreted in human breast milk. Available pharmacodynamic/toxicological data in animals have shown secretion/excretion of cipaglucosidase alfa in milk, see section 5.3. A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from cipaglucosidase alfa in combination with miglustat therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no clinical data on the effects of cipaglucosidase alfa on fertility.

Preclinical data did not reveal any significant adverse findings with cipaglucosidase alfa, see section 5.3.

4.7 Effects on ability to drive and use machines

Cipaglucosidase alfa has 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 cipaglucosidase alfa.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions only attributable to cipaglucosidase alfa were chills (4.0%), dizziness (2.6%), flushing (2.0%), somnolence (2.0%), chest discomfort (1.3%), cough, (1.3%), infusion site swelling (1.3%), and pain (1.3%).

Reported serious adverse reactions only attributable to cipaglucosidase alfa were urticaria (2.0%), anaphylaxis (1.3%), 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 cipaglucosidase alfa in combination with miglustat therapy from the pooled safety analysis of the 3 clinical trials. The total mean duration of exposure was 17.2 months.

Adverse reactions from the clinical trials are listed by MedDRA system organ class in Table 1. The corresponding frequency categories are defined as follows: 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).

Table 1: Summary of adverse reactions from clinical trials with cipaglucosidase alfa-treated subjects

System organ class (SOC)	Frequency	Adverse reaction (preferred term)
Immune system disorders	Common	Anaphylactic reaction‡[1]
	Uncommon	Hypersensitivity
Nervous system disorders	Very common	Headache
	Common	Dizziness*, tremor, somnolence*, dysgeusia
	Uncommon	Balance disorder, burning sensation*, migraine[4], paraesthesia*, presyncope*
Cardiac disorders	Common	Tachycardia[6]
Vascular disorders	Common	Flushing*
	Uncommon	Hypotension, pallor
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea, cough*
	Uncommon	Asthma, oropharyngeal discomfort*, pharyngeal oedema*, wheezing*
Gastrointestinal disorders	Common	Diarrhoea, nausea, abdominal pain[7], flatulence, abdominal distension, vomiting
	Uncommon	Dyspepsia*, oesophageal pain*, oesophageal spasm, oral discomfort*, oral pain, swollen tongue*
Skin and subcutaneous tissue disorder	Common	Urticaria[3], rash[2], pruritus, hyperhidrosis
	Uncommon	Skin discolouration, skin oedema*
Musculoskeletal and connective tissue disorders	Common	Muscle spasms, myalgia, muscular weakness
	Uncommon	Arthralgia, flank pain, muscle fatigue, musculoskeletal stiffness
General disorders and administration site conditions	Common	Fatigue, pyrexia, chills, chest discomfort*, infusion site swelling*, pain*

System organ class (SOC)	Frequency	Adverse reaction (preferred term)
	Uncommon	Asthenia, facial pain, infusion site pain*, malaise*, non-cardiac chest pain, peripheral swelling
Investigations	Common	Blood pressure increased[5]
	Uncommon	Body temperature fluctuation*, lymphocyte count decreased
Injury, poisoning and procedural complications	Uncommon	Skin abrasion*

* Reported with cipaglucosidase alfa only
‡ See below "Infusion-associated reactions".
[1] Anaphylaxis, anaphylactic reaction, and anaphylactoid reaction are grouped under anaphylaxis.
[2] Rash, rash erythematous, and rash macular are grouped under rash.
[3] Urticaria, urticaria rash, and mechanical urticaria 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] Tachycardia and sinus tachycardia are grouped under tachycardia.
[7] Abdominal pain, abdominal pain upper, and abdominal pain lower are grouped under abdominal pain.

Description of selected adverse reactions

Infusion-associated reactions (IARs)
The following IARs were reported in the phase 3 study during the cipaglucosidase alfa infusion or within 2 hours after completion of this 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 phase 3 trial receiving cipaglucosidase alfa and miglustat. 1.3% of patients receiving cipaglucosidase alfa and miglustat discontinued treatment due to IARs (anaphylaxis and chills). Most IARs were mild or moderate in severity and transient in nature.

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

No doses of cipaglucosidase alfa in excess of 20 mg/kg body weight have been studied and no experience with accidental overdose have been observed to inform management of overdose. For management of adverse reactions, see sections 4.4 and 4.8.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Pompe disease is caused by a deficiency of acid-alpha-glucosidase (GAA) that degrades glycogen to glucose in the lysosome. Cipaglucosidase alfa is intended to replace the absent or impaired endogenous enzyme.

Cipaglucosidase alfa is stabilised by miglustat minimising the loss of enzyme activity in the blood during infusion of this hydrolytic glycogen-specific enzyme enriched with 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 which are both required to yield the most mature and active form of the GAA enzyme. Cipaglucosidase alfa then exerts enzymatic activity in cleaving glycogen and reducing intramuscular glycogen, and ameliorating tissue damage.

Clinical efficacy and safety

A 52-week phase 3 randomised, double-blind, active-controlled, international, multi-centre clinical trial was conducted in adult subjects (≥ 18 years) diagnosed with Pompe disease. Subjects were randomised 2:1 to receive 20 mg/kg cipaglucosidase alfa in combination with 195 mg or 260 mg miglustat based on the subject's 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 subjects 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, see Table 2. More than two thirds (67%) of ERT-experienced subjects had been on ERT treatment for more than 5 years prior to entering the phase 3 trial (mean of 7.4 years).

Table 2: Subject demographics and baseline characteristics

Baseline characteristics	**Cipaglucosidase alfa in combination with miglustat n = 85**	**Alglucosidase alfa in combination with placebo n = 37**
Age at informed consent (years), mean (SD)	47.6 (13.3)	45.4 (13.4)

Baseline characteristics	Cipaglucosidase alfa in combination with miglustat n = 85	Alglucosidase alfa in combination with placebo n = 37
Male gender, n %	36 (42.4)	19 (51.4)
Weight (kg), mean (SD)	72.8 (14.7)	79.4 (25.0)
ERT-experienced, n (%)	65 (76.5)	30 (81.1)
Age at first ERT dose (years), mean (SD)	40.8 (12.7)	38.7 (15.1)
6MWD (m), mean (SD)	357.9 (111.8)	351.0 (121.3)
Sitting % FVC, mean (SD)	70.7 (19.6)	69.7 (21.5)

6MWD: 6-minute walk distance; ERT: enzyme replacement therapy; FVC: sitting percent predicted forced vital capacity; SD: standard deviation

Key efficacy endpoints included assessment of 6MWD (primary endpoint), and the sitting percent predicted FVC. Key pharmacodynamic endpoints included serum creatine kinase (CK) and urinary glucose tetrasaccharides (Hex-4).

Motor function

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

All subjects (ERT-experienced and ERT-naïve) treated with cipaglucosidase alfa in combination with miglustat therapy had a mean improvement in walk distance from baseline of 20.0 meters as compared to those treated with alglucosidase alfa-placebo with a mean of 8.3 meters, indicating a cipaglucosidase alfa in combination with miglustat treatment effect of 11.7 meters (95% CI [-1.0, 24.4]; p = 0.07) (Table 3).

The ERT-experienced subjects treated with cipaglucosidase alfa in combination with miglustat therapy (n = 65) had a mean improvement in walk distance from baseline of 15.9 meters as compared to a mean of 1.0 meter for alglucosidase alfa in combination with placebo (n = 30), indicating a cipaglucosidase alfa/miglustat treatment effect of 14.9 meters (95% CI [1.2, 28.6]).

The ERT-naïve subjects treated with cipaglucosidase alfa in combination with miglustat therapy (n = 20) had a mean improvement in walk distance from baseline of 28.5 meters as compared to 52.7 meters for alglucosidase alfa in combination with placebo (n = 7), indicating a cipaglucosidase alfa/miglustat treatment effect of -24.2 meters (95% CI [-60.0, 11.7]).

Table 3: Summary of 6MWD in all subjects at 52 weeks

6MWD (meters)	Cipaglucosidase alfa in combination with miglustat	Alglucosidase alfa in combination with placebo
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)	20.0 (3.5)	8.3 (5.3)
(95% CI)	(13.1, 26.9)	(-2.2, 18.8)

Change to week 52 Diff. of means (SE) (95% CI) 2-sided p value	 11.7 (6.4) (-1.0, 24.4) p = 0.07*

CI: confidence interval; Diff.: difference; SD: standard deviation; SE: standard error
Reported data based on mixed model for repeated measures (MMRM) analysis with actual time point of assessments (ITT-OBS population) excluding outlier in the ITT population.
* Primary endpoint did not achieve superiority.

Pulmonary function

Sitting percent-predicted FVC at 52 weeks
All subjects (ERT-experienced and ERT-naïve) treated with cipaglucosidase alfa in combination with miglustat therapy showed a mean change in FVC from baseline of -1.4% as compared with subjects treated with alglucosidase alfa-placebo of -3.7%, indicating a cipaglucosidase alfa-miglustat treatment effect of 2.3% (95% CI [0.2, 4.4]) (Table 4).

The ERT-experienced subjects treated with cipaglucosidase alfa in combination with miglustat therapy (n = 65) showed a mean change in FVC from baseline of -0.2% as compared with subjects treated with alglucosidase alfa in combination with placebo (n = 30) of -3.8%, indicating a cipaglucosidase alfa-miglustat treatment effect of 3.6% (95% CI [1.3, 5.9]).

The ERT-naïve subjects treated with cipaglucosidase alfa in combination with miglustat therapy (n = 20) showed a mean change in FVC from baseline of -5.2% as compared with subjects treated with alglucosidase alfa-placebo (n = 7) of -2.4%, indicating similar rates of decline of -2.8% difference with a 95% CI (-7.8, 2.3).

Table 4: Summary of percent predicted FVC in all subjects at 52 weeks

Sitting percent predicted FVC	**Cipaglucosidase alfa in combination with miglustat**	**Alglucosidase alfa in combination with 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)	 n = 85 -1.4 (0.6) (-2.5, -0.3)	 n = 37 -3.7 (0.9) (-5.4, -2.0)
Change to week 52 Diff. of means (SE) (95% CI)	 2.3 (1.1) (0.2, 4.4)	

CI: confidence interval; Diff.: difference; SD: standard deviation; SE: standard error
Reported data based on mixed model for repeated measures (MMRM) analysis with actual time point of assessments (ITT-OBS population) excluding outlier in the ITT population.

Secondary endpoints
The observed effects for the secondary endpoints supported the conclusions drawn from the 6MWD and sitting % predicted FVC.

Subjects who were treated with 20 mg/kg cipaglucosidase alfa in combination with the enzyme stabiliser miglustat 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.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with cipaglucosidase alfa in one or more subsets of the paediatric population in the treatment of glycogen storage disease Type II (Pompe disease) (see section 4.2 for information on paediatric use).

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

Cipaglucosidase alfa is not expected to bind to plasma proteins. The mean volume of distribution of cipaglucosidase alfa ranged from 2.0 to 4.7 L. The distribution half-life was increased by 48% following usage of both cipaglucosidase alfa and miglustat. Correspondingly, plasma clearance decreased by 27%.

Following the administration of a single dose of miglustat 260 mg in combination with cipaglucosidase alfa 20 mg/kg in fasting adults with Pompe disease in a phase 1/2 trial, total GAA protein partial $AUC_{tmax-24h}$ (time of maximum concentration at the end of infusion to 24 hours post-start of infusion) increased by 44% relative to cipaglucosidase alfa 20 mg/kg alone.

Cipaglucosidase alfa does not cross the blood-brain barrier.

Elimination

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 pooled population pharmacokinetic analysis, gender, age (18 to 74 years old), and race/ethnicity did not have clinically meaningful effect on the exposure to cipaglucosidase alfa in combination with miglustat. Of the total number of patients treated with cipaglucosidase alfa in

combination with miglustat in clinical trials for LOPD, 17 (11%) were 65 to 74 years of age, and none were 75 years of age and older.

Hepatic impairment
The pharmacokinetics of cipaglucosidase alfa in combination with miglustat therapy have not been evaluated in patients with hepatic impairment.

Renal impairment
No studies with cipaglucosidase alfa in combination with miglustat therapy have been carried out in subjects with impaired renal function. The disposition of cipaglucosidase alfa is not expected to be impacted by renal impairment.

5.3 Preclinical safety data

Nonclinical data for cipaglucosidase alfa revealed no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity, genotoxicity, carcinogenicity, and mutagenicity.

Reproductive and developmental toxicology
There was no effect of cipaglucosidase alfa in combination with miglustat therapy on spermatogenesis in rats.

In a segment II embryo-fetal development study, no adverse findings were observed in pregnant rats or their offspring up to an exposure margin of 15.5-fold and 3.4-fold, respectively, for cipaglucosidase alfa and miglustat based on plasma AUC exposure. However, in rabbits for both miglustat and the combination group (cipaglucosidase alfa with miglustat), maternal effects including decreased food consumption and body weight gains were evident. Cardiovascular malformations and variations were not elevated in the cipaglucosidase alfa groups without miglustat when compared to the control groups. These results indicate that the combination of cipaglucosidase alfa with miglustat resulted in increased cardiovascular malformations (atretic pulmonary trunk, ventricular septum defect, and dilated aortic arch) in rabbits at doses of 8.8-fold and 4.8-fold, respectively, the MRHD (based on mg/kg basis) or 12.1-fold and 2.6-fold, respectively, based on plasma AUC after a single exposure, or 84 and 18.5 based on cumulative exposure for matching human and animal dosing regimens.

In a segment III pre-and post-natal development study in rats, cipaglucosidase alfa alone or in combination with miglustat was administered to pregnant females. Maternal and pup mortality were observed with the combination cipaglucosidase alfa and miglustat, and pup mortality was also increased with cipaglucosidase alfa alone. There was no NOAEL for the combination at exposure margins up to 15.5-fold and 3.4-fold, respectively, for cipaglucosidase alfa and miglustat based on plasma AUC exposure. Evaluation of milk in rats from the combination treatment group showed excretion of miglustat and cipaglucosidase alfa in rat milk. At 3 hours post dose, the ratio of cipaglucosidase alfa exposure in rat milk to plasma was 0.038.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate dihydrate (E331)
Citric acid monohydrate (E330)
Mannitol (E421)
Polysorbate 80 (E433)

6.2 Incompatibilities

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

6.3 Shelf life

Unopened container

3 years

Reconstituted medicinal product

After reconstitution, chemical, physical, and microbiological in-use stability has been demonstrated for 24 hours at 2°C to 8°C.

From a microbiological point of view, the reconstituted product should be used immediately. If not used for dilution immediately, in-use storage times and conditions prior to dilution are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C.

Diluted medicinal product

After dilution after reconstitution, chemical, physical, and microbiological in-use stability has been demonstrated between 0.5 mg/mL and 4 mg/mL for 24 hours at 2°C to 8°C, followed by 6 hours at room temperature (up to 25°C) to allow for infusion.

Use of aseptic techniques

From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, followed by 6 hours at room temperature (up to 25°C) to allow for infusion.

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

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

105 mg of powder for concentrate for solution for infusion in a 20 mL neutral borosilicate clear Type I glass vial sealed with 20 mm chlorobutyl rubber stopper and with an aluminium over seal with dark grey plastic button.

Packs containing 1, 10, and 25 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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.

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 (i.e. approximately 30 minutes at 20°C to 25°C).
- Do not use if the lyophilised powder 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 clear to opalescent, colourless to slightly yellow solution, free of foreign particles, and practically free of particles in the form of white to translucent particles. If upon immediate inspection foreign matter is observed or if the solution is discoloured, do not use.
4. Repeat above steps for the number of vials needed for dilution.

Dilution and preparation of the infusion bag

1. Select an intravenous (IV) bag with sufficient volume to achieve a final target concentration range of 0.5 mg/mL to 4 mg/mL for the diluted cipaglucosidase alfa solution for IV infusion.
2. Remove airspace within the infusion bag. Remove an equal volume of sodium chloride 9 mg/mL (0.9%) solution for injections that will be replaced by the total volume (mL) of reconstituted cipaglucosidase alfa.
3. The reconstituted volume allows accurate withdrawal of 7.0 mL (equal to 105 mg) from each vial. Using a syringe with a needle diameter not larger than 18 gauge, slowly withdraw 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.
4. Slowly inject the reconstituted cipaglucosidase alfa 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.
5. Gently invert or massage the bag to mix the diluted solution. Do not shake or excessively agitate the bag for infusion. Do not use a pneumatic tube to transport the infusion bag.

The infusion solution should be administered as close to after dilution preparation as possible at room temperature, see section 4.2.

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. Storage at room temperature is not recommended, refer to the in-use stability storage conditions. Do not freeze or shake.

The sodium chloride 9 mg/mL (0.9%) solution for injections bag containing the diluted 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 IV-line blocks during infusion, change the filter.

Other medicinal products should not be infused in the same IV line as the diluted cipaglucosidase alfa solution.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

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Ireland

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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1714/001
EU/1/22/1714/002
EU/1/22/1714/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance
WuXi Biologics Co., Ltd.
108 Meiliang Road, Mashan, Binhu District, WuXi, 214092, China

Name and address of the manufacturer responsible for batch release

Manufacturing Packaging Farmaca (MPF) B.V.
Neptunus 12, Heerenveen, 8448CN, Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.
The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Educational materials for home infusion

The MAH must agree on the content and format of the educational materials for use of Pombiliti in home infusion, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational materials for the use of Pombiliti in home infusion are aimed at providing guidance on how to manage the risk of infusion-related reactions including allergic-type hypersensitivity reactions in a home setting.

The MAH shall ensure that in each Member State where Pombiliti is marketed, all healthcare professionals and patients/caregivers who are expected to prescribe, dispense, or use Pombiliti have access to/are provided with the following educational package:
- Home infusion guide for healthcare professionals
- Patient/caregiver's guide including an infusion diary

The home infusion guide should contain the following key elements:
- Details on the preparation and administration of Pombiliti, including all the steps of preparation, reconstitution, dilution, and administration;
- Guidance on the medical evaluation of the patient prior to administration of the infusion at home;
- Information on signs and symptoms related to IARs and recommended actions for the management of the adverse drug reactions (ADRs) when symptoms occur.

The patient/caregiver's guide should contain the following key elements:
- Information on signs and symptoms related to IARs and recommended actions for the management of the ADRs when symptoms occur.
- An Infusion Diary that can be used to record the infusions and document any product-related IARs, including allergic-type hypersensitivity reactions before, during or after the infusion.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Pombiliti 105 mg powder for concentrate for solution for infusion
cipaglucosidase alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 105 mg of cipaglucosidase alfa.
After reconstitution, the solution contains 15 mg of cipaglucosidase alfa per mL.

3. LIST OF EXCIPIENTS

Excipients:
Sodium citrate dihydrate (E331)
Citric acid monohydrate (E330)
Mannitol (E421)
Polysorbate 80 (E433)
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

powder for concentrate for solution for infusion

1 vial
10 vials
25 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For single-use only

Intravenous use after reconstitution and dilution

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

ATTENTION: Only use Pombiliti with miglustat 65 mg hard capsules.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C).
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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Block 1, Blanchardstown Corporate Park,
Ballycoolin Road, Blanchardstown,
Dublin D15 AKK1, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1714/001 1 vial
EU/1/22/1714/002 10 vials
EU/1/22/1714/003 25 vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL INTERMEDIATE PACKAGING

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

Pombiliti 105 mg
powder for concentrate
cipaglucosidase alfa

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

For single-use only.
IV use after reconstitution and dilution

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

ATTENTION: Only use Pombiliti with miglustat 65 mg hard capsules.

Store in a refrigerator. Keep the vial in the outer carton in order to protect from light.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Pombiliti 105 mg powder for concentrate for solution for infusion
cipaglucosidase alfa

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Pombiliti is and what it is used for

What Pombiliti is
Pombiliti is a type of 'enzyme-replacement therapy' (ERT) that is used in the treatment of late-onset Pompe disease in adults. It contains the active substance 'cipaglucosidase alfa'.

What it is used for
Pombiliti is always used with another medicine called miglustat 65 mg hard capsules. It is very important that you also read the package leaflet of miglustat 65 mg hard capsules.

If you have any questions about your medicines, please ask your doctor or pharmacist.

How Pombiliti works
People with Pompe disease have low levels of the enzyme acid alpha-glucosidase (GAA). This enzyme helps control levels of glycogen (a type of carbohydrate) 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 enters the muscle cells that are affected by Pompe disease. When in the cells, the medicine works like GAA to help break down glycogen and control its levels.

2. What you need to know before you are given Pombiliti

You must not be given Pombiliti
- If you have ever had life-threatening hypersensitivity reactions to:
  - cipaglucosidase alfa
  - miglustat
  - any of the other ingredients of this medicine (listed in section 6).

- If a previous infusion had to be stopped and could not be restarted due to life threatening hypersensitivity reactions.

Warnings and precautions
Talk to your doctor, pharmacist, or nurse before using Pombiliti.

Speak to your doctor or nurse immediately if these apply to you, if you think it might apply to you or if you have ever had any such reactions with another enzyme replacement therapy (ERT):
- allergic reactions, including anaphylaxis (a severe allergic reaction) – see section 4 under 'Possible side effects', below for symptoms of life-threatening reactions.
- infusion-associated reaction while you are receiving the medicine or in the few hours afterwards - see section 4 under 'Possible side effects', below for symptoms of life-threatening reactions.

Inform your doctor if you have a history of heart or lung disease. These conditions may worsen during or immediately after your infusion with Pombiliti. Tell a doctor or nurse immediately if you are experiencing shortness of breath, cough, rapid or irregular heartbeat or any other effects from these conditions.

Also tell your doctor if you have swelling in your legs or widespread swelling of your body, severe skin rash or frothy urine when passing water. Your doctor will decide if your Pombiliti infusion should stop, and the doctor will give you appropriate medical treatment. Your doctor will also decide if you can continue receiving Pombiliti.

Pre-treatment medications
Your doctor 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.

Children and adolescents
This medicine should not be given to patients under the age of 18 years old. This is because the effects of Pombiliti in conjunction with miglustat in this age group are not known.

Other medicines and Pombiliti
Tell a doctor or nurse if you are using, have recently used, or will be using any other medicines. This includes medicines obtained without a prescription, including herbal medicines.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, do not take this medicine but talk to your doctor or pharmacist immediately for advice before using this medicine.

There is no experience with the use of Pombiliti in combination with miglustat during pregnancy.

- You should not receive Pombiliti and / or take miglustat 65 mg hard capsules if you are pregnant. Be sure to tell your doctor immediately if you get pregnant, think that you may be pregnant, or if you are planning to become pregnant. There may be risks to the unborn baby.
- Pombiliti in combination with miglustat should not be given to women who are breast-feeding. A decision will need to be made whether to stop treatment or to stop breast-feeding.

Contraception and fertility
Female patients of childbearing potential must use reliable birth control methods during and for 4 weeks after stopping both medicines.

Driving and using machines
You may feel dizzy, sleepy, or have low blood pressure (hypotensive) after having Pombiliti or pre-treatment medicines. If this happens, do not drive or use any tools or machines.

Pombiliti contains sodium
This medicinal product contains 10.5 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 0.52% of the recommended maximum daily dietary intake of sodium for an adult.

3. How Pombiliti is given

Pombiliti is given to you by a doctor or nurse. It is given through a drip into a vein. This is called an intravenous infusion.

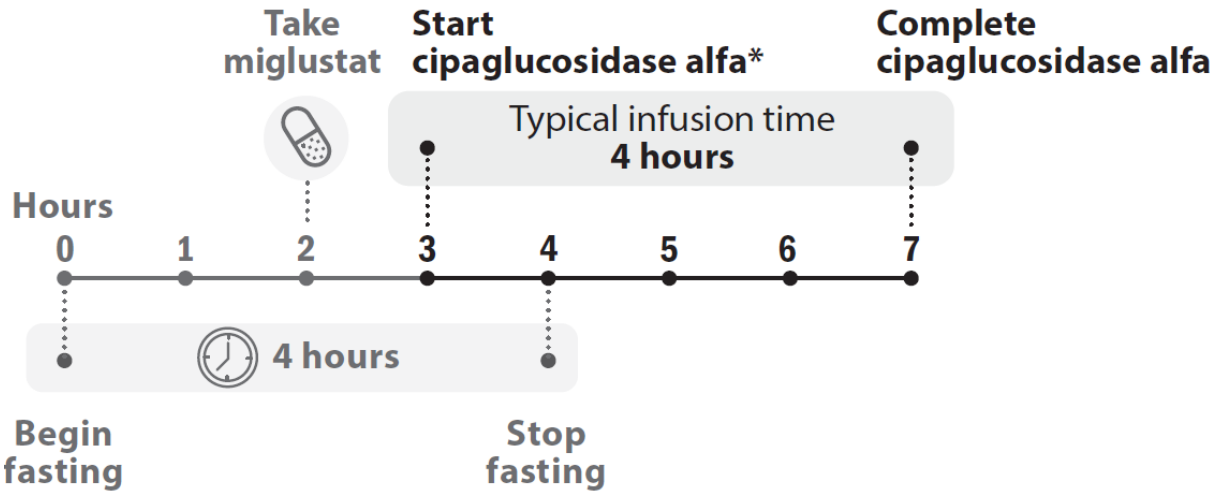
Talk to your doctor if you would like to be treated at home. Your doctor will decide upon evaluation if it is safe for you to have home infusion of Pombiliti. If you get any side effects during an infusion of Pombiliti, your home infusion staff member may stop the infusion and start appropriate medical treatment.

Pombiliti should be used in conjunction with miglustat. You can only use miglustat 65 mg capsules with cipaglucosidase alfa. Do **NOT** use miglustat 100 mg capsules (different product). Follow your doctor's instructions and read the package leaflet of miglustat 65 mg hard capsules for their recommended dose.

How much Pombiliti is given
The amount of medicine that you will be given is based on your weight. The recommended dose is 20 mg for each kg of body weight.

When and for how long Pombiliti is given
- You will be treated with Pombiliti once every other week. Miglustat 65 mg capsules are taken on the same day as Pombiliti. Refer to the package leaflet of miglustat 65 mg hard capsules for information on how to take miglustat.
- The cipaglucosidase alfa infusion should start 1 hour after taking miglustat 65 mg hard capsules.
  - In the event of a delay, the start of infusion should not exceed 3 hours from taking miglustat.
- The infusion of cipaglucosidase alfa lasts approximately 4 hours.

Figure 1. Dose timeline



* The cipaglucosidase alfa infusion should start 1 hour after taking miglustat capsules. In the event of infusion delay, the start of infusion should not exceed 3 hours from taking miglustat.

Switching from another enzyme replacement therapy (ERT)
If you are currently being treated with another ERT:
- Your doctor will tell you when to stop the other ERT before starting Pombiliti.
- Tell your doctor when you completed your last dose.

If you are given more Pombiliti than you should
If you have difficulty breathing, feel swollen or bloated, or your heart is racing, you may have been given too much Pombiliti; tell your doctor straight away. Excessive rate of infusion of Pombiliti could result in symptoms related to too much fluid in the body, such as shortness of breath, rapid heart rate, or widespread swelling of the body.

If you miss your dose of Pombiliti
If you have missed an infusion, please contact your doctor or nurse as soon as possible to reschedule Pombiliti in combination with miglustat 24 hours after miglustat was last taken.

If you stop receiving Pombiliti
Speak to your doctor if you wish to stop Pombiliti treatment. The symptoms of your disease may worsen if you stop treatment.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Pombiliti is used with miglustat, 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 doctor immediately if you get an infusion-associated reaction or an allergic reaction. Some of these reactions may become serious and life-threatening. Your doctor may give you medicines before your infusion to prevent these reactions.

Infusion-associated reactions
Most infusion-associated reactions are mild or moderate. Symptoms of infusion-associated reaction may include difficulty breathing, bloating, fever, chills, dizziness, skin redness, itchy skin, and rash.

Allergic reactions
Allergic reactions may include symptoms such as rash anywhere on the body, puffy eyes, prolonged difficulty breathing, cough, swelling of the lip, tongue, or throat, itchy skin, and hives.

Very common (may affect more than 1 in 10 people)
- Headache

Common (may affect up to 1 in 10 people)
- Cough
- Sudden reddening of the face, neck, or upper chest
- Pain in chest
- Rash, itching
- Rise in blood pressure
- Sweating
- Bloating
- Passing gas or wind
- Loose, runny stools
- Vomiting
- Nausea
- Fever or chills
- Hives
- Swelling or pain in the body area where needle was inserted
- Muscle cramps, muscle pain, muscle weakness
- Involuntary shaking of one or more parts of the body
- Increased sweating

- Pain
- Altered sense of taste
- Feeling tired all the time, or feeling sleepy
- Shortness of breath

Uncommon (may affect up to 1 in 100 people)
- Breathing difficult and triggers coughing, a whistling sound (wheezing) when you breathe out, and shortness of breath (asthma)
- Allergic reaction
- Swelling in the hands, feet, ankles, legs
- Swelling of the skin
- Indigestion
- Belly pain
- Constant feeling of being tired
- Sore or irritated throat
- Painful and abnormal contractions of the throat
- Mouth irritation
- Mouth pain or discomfort in the back of the mouth
- Pain in the cheek, gums, lips, chin
- Loss of strength and energy, feeling weak
- Feeling of uneasiness, overall feeling of being sluggish
- Burning sensation
- Scratch or damage to the skin
- Changes in body temperature
- Decrease in a type of white blood cell – shown in tests
- Feeling drowsy
- Feeling dizzy
- Pain in joints
- Pain in the area between the hip and rib
- Muscle fatigue
- Increased rigidity of muscles
- Cannot hold or maintain balance
- Low blood pressure
- Feeling of near fainting
- Pain in one or both sides of the head, throbbing pain, aura, eye pain, sensitivity to light (migraine)
- Skin discolouration

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Pombiliti

Your doctor, pharmacist, or nurse is responsible for storing this medicine and disposing of any opened vials correctly. The following information is intended for healthcare professionals.

Keep this medicine out of the sight and reach 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.

Unopened vials: Store in the refrigerator (2°C - 8°C). Keep the vial in the outer carton in order to protect from light.

After dilution, an immediate use is recommended. However, storage of the intravenous bag with Pombiliti has been demonstrated for 6 hours at 20°C - 25°C and 24 hours at 2°C - 8°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines that you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Pombiliti contains
The active substance is cipaglucosidase alfa. One vial contains 105 mg of cipaglucosidase alfa. After reconstitution, the solution in the vial contains 15 mg of cipaglucosidase alfa per mL. The recommended final concentration of cipaglucosidase alfa diluted into the intravenous bag ranges from 0.5 mg/mL to 4 mg/mL.

The other ingredients are:
- Sodium citrate dihydrate (E331)
- Citric acid monohydrate (E330)
- Mannitol (E421)
- Polysorbate 80 (E433)

What Pombiliti looks like and contents of the pack

Pombiliti is a white to slightly yellowish powder. After reconstitution, it appears as a clear to opalescent, colourless to slightly yellow solution, free of foreign particles, practically free of particles in the form of white to translucent particles. The reconstituted solution must be further diluted into an intravenous bag for infusion.

Pombiliti is a powder for concentrate for solution for infusion in a vial

Packs of 1 vial, 10 vials, or 25 vials

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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Manufacturer

Manufacturing Packaging Farmaca (MPF) B.V.
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

The following information is intended for healthcare professionals only:

Instructions for use – reconstitution, dilution, and administration

Pombiliti must be reconstituted with water for injection, then diluted with sodium chloride 9 mg/mL (0.9%) solution for injections and then administered by intravenous infusion. Reconstitution and dilution should be performed in accordance with good practice rules, particularly for the respect of asepsis.

Because this medicine is a protein, particle formation may occur in the reconstituted solution and final diluted infusion bags. Therefore, a 0.2-micron low protein binding in-line filter should be used for administration. It was demonstrated that the use of a 0.2 micron in-line filter removes visible particles and does not result in an apparent loss of protein or activity.

Determine the number of vials to be reconstituted based on the individual patient's dose regimen (mg/kg) and remove the required vials from the refrigerator in order to allow them to reach room temperature (approximately 30 minutes). Each vial of Pombiliti is for single use only.

Use aseptic technique.

Reconstitution

Reconstitute each 105 mg per vial of Pombiliti with 7.2 mL water for injections using a syringe with a needle diameter not larger than 18 gauge. Add the water for injections by slow drop-wise addition down the side of the vial and not directly onto the lyophilised powder. Tilt and roll each vial gently. Do not invert, swirl, or shake the vial. The extraction volume appears as a clear to opalescent, colourless to slightly yellow solution, free of foreign particles, and practically free of particles in the form of white to translucent particles. Perform an immediate inspection of the reconstituted vials for particulate matter and discolouration. Do not use if upon immediate inspection foreign particles other than those described above are observed, or if the reconstituted solution is discoloured. The pH of the reconstituted solution is approximately 6.0.

After reconstitution it is recommended to promptly dilute the vials (see below).

Dilution

When reconstituted as above, the reconstituted solution in the vial contains 15 mg cipaglucosidase alfa per mL. The reconstituted volume allows accurate withdrawal of 7.0 mL (equal to 105 mg) from each vial. This should then be further diluted as follows: Slowly withdraw the reconstituted solution from each vial, including less than the 7.0 mL for the partial vial, until the volume for the patient's dose is obtained using a syringe with a needle diameter not larger than 18 gauge. The recommended final concentration of cipaglucosidase alfa in the infusion bags ranges from 0.5 mg/mL to 4 mg/mL. Remove airspace within the infusion bag. Also remove an equal volume of sodium chloride 9 mg/mL (0.9%) solution for injections, that will be replaced with reconstituted Pombiliti. Slowly inject the reconstituted Pombiliti directly into the sodium chloride 9 mg/mL (0.9%) solution for injections. Gently invert or massage the infusion bag to mix the diluted solution. Do not shake or excessively agitate the infusion bag.

The final infusion solution should be administered as close to preparation time as possible.

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

Administration

The Pombiliti infusion should start 1 hour after taking miglustat capsules. In the event of infusion delay, the start of infusion should not exceed 3 hours from taking miglustat.

The recommended dose regimen of Pombiliti is 20 mg/kg of body weight administered once every other week as an intravenous infusion.

Infusions should be administered incrementally. It is recommended that the infusion begin at an initial rate of 1 mg/kg/hr and be gradually increased by 2 mg/kg/hr every 30 minutes if there are no signs of IARs (infusion-associated reactions) until a maximum rate of 7 mg/kg/hr is reached.