swissmedic

Date: 26 August 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Pombiliti

International non-proprietary name: cipaglucosidase alfa
Pharmaceutical form: powder for concentrate for solution for infusion
Dosage strength(s): 105 mg
Route(s) of administration: parenteral
Marketing authorisation holder: Amicus Therapeutics Switzerland GmbH
Marketing authorisation no.: 67804
Decision and decision date: approved on 4 July 2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LOPD	late-onset Pompe disease
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for cipaglucosidase alfa in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 of the TPA.
Orphan drug status was granted on 19 March 2020.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

2.2 Indication and dosage

2.2.1 Requested indication

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) (LOPD).

2.2.2 Approved indication

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).

2.2.3 Requested dosage

Cipaglucosidase alfa must be used in combination with miglustat 65 mg hard capsules. Because of this, the human medicinal product Information for miglustat 65 mg hard capsules should be consulted before administering cipaglucosidase alfa with regard to the number of capsules (based on body weight), dose time, and fasting requirements.

The recommended dose of cipaglucosidase alfa is 20 mg/kg 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.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	12 June 2023
Formal control completed	28 June 2023
Preliminary decision	17 November 2023
Response to preliminary decision	16 January 2024
Labelling corrections	25 March 2024
Response to labelling corrections	24 April 2024
Final decision	4 July 2024
Decision	approval

Swissmedic has not assessed the primary data (e.g. study reports) submitted with this application and relies for its decision on the assessment of the foreign reference authority, the EMA. This SwissPAR relates to the publicly available assessment report for Pombiliti issued by the EMA.

3 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The SwissPAR relating to quality aspects refers to the publicly available assessment report Pombiliti (cipaglucosidase alfa) EMA/950090/2022, issued by the EMA.

4 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The nonclinical aspects in this SwissPAR refer to the publicly available assessment report Pombiliti (cipaglucosidase alfa) EMA/950090/2022, issued by the EMA.

5 Clinical aspects

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The clinical aspects in this SwissPAR refer to the publicly available assessment report Pombiliti (cipaglucosidase alfa) EMA/950090/2022, issued by the EMA.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Pombiliti was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Pombiliti®

Composition

Active substances

Cipaglucosidase alfa*.

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

Excipients

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

Each vial contains 10.5 mg of sodium.

Pharmaceutical form and active substance quantity per unit

Powder for concentrate for solution for infusion. For intravenous infusion.

White to slightly yellowish lyophilised powder.

One vial contains 105 mg of cipaglucosidase alfa.

After reconstitution of each vial (see section “Instructions for handling”), the concentrated solution contains 15 mg of cipaglucosidase alfa per mL.

Indications/Uses

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).

Dosage/Administration

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

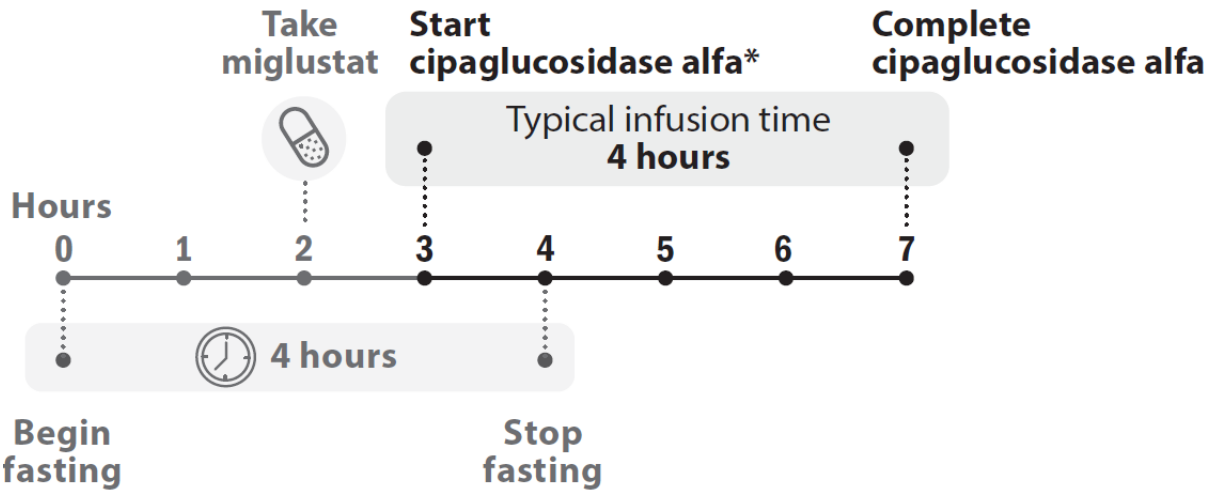
Cipaglucosidase alfa must be used in combination with miglustat 65 mg hard capsules. Because of this, the information for miglustat 65 mg hard capsules should be consulted before taking cipaglucosidase alfa concerning number of capsules (based on body weight), dose time, and fasting.

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Usual dosage

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 “Warnings 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 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 “Warnings and precautions”).

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 dosage instructions

Patients with hepatic and renal disorders

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.

Elderly patients

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 “Pharmacokinetics”).

Children and adolescents

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.

Mode 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 “Contraindications” and “Warnings and precautions”).

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 "Warnings and precautions").

Subsequent infusions may need to occur in a hospital or in an appropriate setting of outpatient care until no such adverse reaction is present. Dose and infusion rate must not be changed without consulting the responsible 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 "Instructions for handling").

Contraindications

- Life-threatening hypersensitivity to the active substance, or to any of the excipients. when rechallenge was unsuccessful, see sections "Warnings and precautions" and "Undesirable effects".

- Contraindication to miglustat.

Warnings and precautions

Anaphylaxis and infusion-associated reactions

Serious anaphylaxis and IARs have occurred in some patients during infusion and following infusion with cipaglucosidase alfa (see section “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 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, equivalent to 0.52% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Interactions

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.

Pregnancy, lactation

Contraception in women

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 “Preclinical data”). 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. Experimental animal studies with cipaglucosidase alfa in combination with miglustat as well as with miglustat alone have shown reproductive toxicity (see section “Preclinical data”).

The potential risk to humans is unknown. Miglustat crosses the placental barrier. Cipaglucosidase alfa in combination with miglustat should not be taken during pregnancy.

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 (see section “Preclinical data”). 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 associated with cipaglucosidase alfa alone. Increased pre-implantation loss was observed in female rats with cipaglucosidase alfa in combination with miglustat and miglustat alone (see section "Preclinical data").

Effects on ability to drive and use machines

Cipaglucosidase alfa has a minor influence on the ability to drive and 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.

Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions attributable to cipaglucosidase alfa and miglustat combination were headache (7.3%), abdominal pain (4.0%), fatigue (4.0%), diarrhoea (3.3%), muscle spasms (3.3%), nausea (2.6%), rash (2.0%), abdominal distension (2.0%), vomiting (2.0%), myalgia (2.0%), tachycardia (2.0%), dysgeusia (1.3%), pyrexia (1.3%), flatulence (1.3%), hyperhidrosis (1.3%), muscular weakness (1.3%), pruritis (1.3%), tremor (1.3%), and urticaria (1.3%).

The most commonly reported adverse reactions only attributable to cipaglucosidase alfa were headache (6.6%), fatigue (4.0%), pyrexia (4.0%), rash (3.3%), chills (3.3%), nausea (3.3%), urticaria (3.3%), dyspnoea (2.6%), dizziness (2.6%), flushing (2.0%), pruritis (2.0%), somnolence (2.0%), abdominal pain (1.3%), blood pressure increased (1.3%), chest discomfort (1.3%), cough (1.3%), myalgia (1.3%), pain (1.3%), and infusion site swelling (1.3%).

The most commonly reported adverse reactions only attributable to miglustat 65 mg were diarrhoea (5.3%), nausea (3.3%), abdominal pain (2.0%), abdominal distension (1.3%), flatulence (1.3%), muscle spasms (1.3%), constipation (1.3%), and tremor (1.3%).

Reported serious adverse reactions attributable to cipaglucosidase alfa and miglustat combination were anaphylaxis (0.7%), hypotension (0.7%), and urticaria (0.7%).

Reported serious adverse reactions only attributable to cipaglucosidase alfa were urticaria (1.3%), anaphylaxis (0.7%), dyspnoea (0.7%), pyrexia (0.7%), wheezing (0.7%), flushing (0.7%), cough (0.7%), pharyngeal oedema (0.7%), presyncope (0.7%), and chills (0.7%).

No serious adverse reactions were attributed to miglustat only.

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, < 1/10), uncommon (≥ 1/1 000, < 1/100).

Table 1: Summary of adverse reactions from clinical trials with cipaglucosidase alfa/miglustat-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 (12.6%)
	Common	Dizziness*, tremor, somnolence*, dysgeusia
	Uncommon	Balance disorder, burning sensation*, migraine[4], paraesthesia*, presyncope*
Cardiac disorders	Common	Tachycardia[5]
Vascular disorders	Common	Flushing*, hypertension
	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[6], flatulence, abdominal distension, vomiting, 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, 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*
	Uncommon	Asthenia, facial pain, feeling jittery†, infusion site pain*, malaise*, non-cardiac chest pain, peripheral swelling, body temperature fluctuation*
Blood and lymphatic system disorders	Uncommon	Lymphocyte count decreased, thrombocytopenia†
Injury, poisoning and procedural complications	Uncommon	Skin abrasion*

* Reported with cipaglucosidase alfa only

† Reported with miglustat 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] Tachycardia and sinus tachycardia are grouped under tachycardia.

[6] Abdominal pain, abdominal pain upper, and abdominal pain lower are grouped under abdominal pain.

Description of specific adverse reactions and additional information

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 “Warnings and precautions”).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

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 “Warnings and Precautions” and “Undesirable effects”).

Properties/Effects

ATC code

A16AB23

Mechanism of action/Pharmacodynamics

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[1] enriched with bis-M6P N-glycans for high affinity cation-independent mannose-6-phosphate receptor (CI-MPR) binding[1]. 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[1,3]. Cipaglucosidase alfa then exerts enzymatic activity in cleaving glycogen and reducing intramuscular glycogen, and ameliorating tissue damage.[1]

Clinical efficacy

A 52-week phase 3 randomised, double-blind, active-controlled, international, multicentre-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)
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 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)	 n = 85 20.0 (3.5) (13.1, 26.9)	 n = 37 8.3 (5.3) (-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.

Pharmacokinetics

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.

Metabolism

Not applicable

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.

Kinetics in specific patient groups

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.

Preclinical data

Nonclinical data for cipaglucosidase alfa reveal no special hazard for humans based on conventional studies of safety pharmacology, and single and repeated dose toxicity. No genotoxicity and carcinogenicity studies have been conducted with cipaglucosidase alfa.

Reproductive and developmental toxicology

There was no effect of cipaglucosidase alfa alone or in combination with miglustat therapy on spermatogenesis in rats.

In a study of fertility and early embryonic development study in rats, increased pre-implantation loss was observed with miglustat alone (60 mg/kg) and in the combination treatment group (cipaglucosidase alfa 400 mg/kg with oral miglustat 60 mg/kg) and was considered miglustat-related. There was no no-observed-adverse-effect-level (NOAEL) for this effect in the combination group.

In a segment II embryo-fetal development study, no adverse findings directly attributed to cipaglucosidase alfa or miglustat 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. The combination of cipaglucosidase alfa with miglustat resulted in increased cardiovascular malformations in rabbit fetuses (atretic pulmonary trunk, ventricular septum defect, and dilated aortic arch) and maternal exposure was 12.1 times and 2.6 times the maximum recommended human dose (MRHD) based on plasma AUC after a single exposure, or 84 times and 18.5 times the MRHD, respectively, based on cumulative exposure for matching human and animal dosing regimens. Cardiovascular malformations and variations were not elevated in the cipaglucosidase alfa groups without miglustat when compared to the control groups.

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. Increased 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 secretion of miglustat and excretion of cipaglucosidase alfa in rat milk. At 3 hours post dose, the ratio of cipaglucosidase alfa exposure in rat milk to plasma was 0.038.

Other information

Incompatibilities

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

Shelf life

Do not use this medicine after the expiry date marked as "EXP" on the pack.

Shelf life after opening

Reconstituted medicinal product

After reconstitution, chemical, physical, and microbiological in-use stability has been demonstrated for 24 hours at 2°C to 8°C. For microbiological reasons, the ready-to-use preparation should be used immediately after reconstitution. If not used immediately for dilution, in-use storage times and conditions before dilution are the responsibility of the user. The reconstituted medicinal product should stored at 2°C to 8°C for a maximum of 24 hours.

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.

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

Special precautions for storage

Store in the refrigerator (2-8°C).

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

Keep out of the reach of children.

For storage conditions after reconstitution and dilution of the medicinal product (see section “Shelf life after opening”).

Instructions for handling

A detailed leaflet for use can be found at the end of the Summary of Product Characteristics.

Authorisation number

67804 (Swissmedic)

Packs

Packs containing 1, 10, and 25 vials [A].

Marketing authorisation holder

Amicus Therapeutics Switzerland GmbH
Seefeldstrasse 69
CH-8008 Zürich
Schweiz

Date of revision of the text

November 2023

Instructions for 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°C to 8°C) and allowed to come to room temperature (i.e. approximately 30 minutes at 20°C to 25°C).
- Do not use if the 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. The pH of the reconstituted solution is about 6.0.
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 airspace 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 “Dosage/Administration”).

Preparing for administration

If it is not possible to start the infusion following dilution, the diluted solution is stable for up to 24 hours refrigerated at 2°C to 8°C. 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.

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 infusion-associated reactions (IARs) until a maximum rate of 7 mg/kg/hr is reached.

Disposal

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