Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed medicines and medicines used outside their licence, to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life-threatening conditions where there are no adequate treatment options. More information about the scheme can be found here:
http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the EAMS medicine. This medicine does not yet have a licence (marketing authorisation) and is to be used in combination with (an)other medicine(s) prescribed outside their licence. The information is provided to assist physicians in prescribing unlicensed medicines. Guidance on prescribing unlicensed medicines can be found on the GMC webpage:
https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

The scientific opinion is based on assessment of the information supplied to the MHRA on the benefits and risks of this promising new medicine used in combination therapy. As such, this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to license such a medicine, nor should it be regarded as an authorisation to sell or supply such a medicine. A positive scientific opinion is not a recommendation for use of the medicine and should not be interpreted as such. Under EAMS the risk and legal responsibility for prescribing a 'special' remains with the physician, and the opinion and EAMs documentation published by the MHRA are intended only to inform physicians' decision making and not to recommend use. An EAMS scientific opinion does not affect the civil liability of the manufacturer or any physician in relation to the product.

Healthcare professionals should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Scientific opinion period: The MHRA will withdraw the EAMS positive scientific opinion when a marketing authorisation (drug licence) is issued for the EAMS product covering the EAMS indication, or if following scientific assessment, the EAMS criteria are considered to be no longer met.

Treatment protocol update(s): In case of substantial new efficacy or safety data, the treatment protocol may need to be updated.

Contact information regarding queries on using this EAMS medicine can be found at the end of this document.

1. NAME OF THE MEDICINAL PRODUCT

Cipaglucosidase alfa 105 mg powder for concentrate for solution for infusion
Miglustat 65 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cipaglucosidase alfa: One vial contains 105 mg of cipaglucosidase alfa.

After reconstitution in the vial, the solution contains 15 mg of cipaglucosidase alfa* per mL and after dilution in the IV bag, the concentration varies from 0.5 mg to 4 mg per mL.

*Human acid α-glucosidase is produced in Chinese hamster ovary cells (CHO) by recombinant DNA technology.

Miglustat: Each capsule contains 65 mg of miglustat.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cipaglucosidase alfa:
powder for concentrate for solution for infusion
white to off-white lyophilised cake or powder

Miglustat:
size 2 hard capsule (6.4x18.0 mm) with a grey opaque cap and white opaque body with “AT2221” printed in black on the body, containing white to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cipaglucosidase alfa in conjunction with miglustat is indicated in the long-term treatment of adult symptomatic patients with confirmed diagnosis of late-onset Pompe disease (acid α-glucosidase [GAA] deficiency) who have received enzyme replacement therapy with alglucosidase alfa for ≥ 2 years.

4.2 Posology and method of administration

Posology

Treatment with miglustat and cipaglucosidase alfa should be supervised by healthcare professionals experienced in the management of late-onset Pompe disease (LOPD).

Patient response to treatment should be routinely evaluated based on a comprehensive evaluation of all clinical manifestations of the disease.

Miglustat and cipaglucosidase alfa recommended frequency of administration is every-other-week.

Miglustat

For patients weighing ≥ 50 kg, the recommended dose is 4 capsules of 65 mg (260 mg total).
For patients weighing ≥ 30 kg to < 50 kg, the recommended dose is 3 capsules of 65 mg (195 mg total).

Cipaglucosidase alfa

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

Special populations

Elderly (≥65 years)

There is limited experience with the use of miglustat in conjunction with cipaglucosidase alfa therapy. Caution should be used when treating this special population.

Renal impairment

The safety and efficacy of miglustat in conjunction with cipaglucosidase alfa therapy have not been evaluated in patients with renal impairment. No dose adjustment is required.

Hepatic Impairment

The safety and efficacy of miglustat in conjunction with cipaglucosidase alfa therapy have not been evaluated in patients with hepatic impairment. No dose adjustment is required.

Paediatric population

The safety and efficacy of miglustat in conjunction with cipaglucosidase alfa therapy have not been evaluated in paediatric patients < 18 years.

Method of administration

Miglustat

Miglustat is for oral use.

Miglustat capsule should be taken on an empty stomach. Patients should fast 2 hours before and 2 hours after taking miglustat.

Capsules should be swallowed whole with water, carbonated water, tea or coffee.

Miglustat should be taken 1 hour (between 50 to 90 minutes) before the start and without delay of the cipaglucosidase alfa infusion. In the event of cipaglucosidase alfa infusion delay, the start of infusion should not exceed 3 hours from the oral administration of miglustat.

Cipaglucosidase alfa

Cipaglucosidase alfa should be administered as an intravenous infusion using an infusion pump.

The patient should be observed during and until infusion is complete.

Infusion of the 20 mg/kg dose is normally administered over the course of 4 hours if tolerated. The infusion rate may be slowed or temporarily stopped in the event of mild to moderate infusion-associated reactions (IARs) as deemed appropriate by the treating healthcare professional. In the event of severe hypersensitivity, anaphylaxis, serious or severe IARs, administration should immediately be discontinued and appropriate medical treatment should be initiated (see sections 4.3 and 4.4).

An infusion should be administered in a stepwise manner. It is recommended that the infusion begin at an initial rate of 1 mg/kg/h and be gradually increased by 2 mg/kg/hr approximately every 30 minutes if there are no signs of IARs until a maximum rate of 7 mg/kg/h is reached. The rate of infusion should be guided by the patient's previous experience during infusion.

For instructions on reconstitution and dilution of the medicinal product before administration (see section 6.6).

Switching patients on another enzyme replacement therapy

After completing the patient's administration of another enzyme replacement therapy (ERT), the patient can be started with miglustat/cipaglucosidase alfa treatment at the next scheduled dosing time (i.e., approximately two weeks after the last ERT administration).

Patients who have switched from another ERT to the miglustat/cipaglucosidase alfa therapy should continue with their premedications used with the other ERT therapy. Depending on tolerability, premedication may be modified. Premedication with corticosteroids, antihistamines, and paracetamol, and/or treatment with corticosteroids or antihistamines may be administered separately to assist with signs and symptoms related to infusion-associated reactions (IARs) and hypersensitivity reactions (see section 4.4).

4.3 Contraindications

Patients with a history of life-threatening infusion-associated reactions/hypersensitivity (e.g., anaphylaxis, anaphylactoid reaction, severe cutaneous reactions) to alglucosidase alfa, cipaglucosidase alfa, miglustat or other iminosugars, or to any of the excipients listed in section 6.1, when re-challenge was unsuccessful (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

General
In order to improve the traceability of biological medicinal products, the EAMS (early access to medicines scheme) and batch numbers of the administered product should be clearly recorded in the patient file.

Infusion-associated reactions / hypersensitivity reactions

Infusion-associated reactions have been reported during infusion and following infusion (see section 4.8). The majority of IARs were reported within 24 hours of infusion. In the clinical studies, some patients were pre-treated with antihistamines, antipyretics and/or corticosteroids. Infusion-associated reactions can occur in some patients after receiving antihistamines, antipyretics and/or corticosteroids. IARs including life-threatening anaphylactoid reaction and hypersensitivity reactions have been reported with ERT medicine in the same pharmacologic drug class as cipaglucosidase alfa.

Mild and transient effects may not require medical treatment or discontinuation of the cipaglucosidase alfa infusion. Reduction of the infusion rate, temporary interruption of the infusion, or pre-treatment, generally with oral antihistamine and/or antipyretics and/or corticosteroids, has effectively managed most infusion-associated reactions. Administer antihistamines, corticosteroids, intravenous fluids, bronchodilators and/or oxygen, when clinically indicated. Because of the potential for severe infusion-associated reactions, appropriate medical support measures, including cardiopulmonary resuscitation equipment should be readily available when cipaglucosidase alfa is administered.

If severe hypersensitivity, anaphylaxis, serious or severe IARs occur, infusion of cipaglucosidase alfa should be immediately discontinued and appropriate medical treatment should be initiated. The current medical standards for emergency treatment of anaphylactic reactions are to be observed. The risks and benefits of re-administering cipaglucosidase alfa following anaphylaxis or severe hypersensitivity reaction should be considered.

Patients who have experienced IARs (and in particular anaphylactic reactions) should be treated with caution when re-administering cipaglucosidase alfa.

Patients with advanced Pompe disease may have compromised cardiac and respiratory function, which may predispose them to a higher risk of severe complications from infusion associated reactions. Therefore, these patients should be monitored more closely during administration of cipaglucosidase alfa.

Immune-mediated reactions

No events consistent with immune-mediated reactions were identified in patients treated with cipaglucosidase alfa in conjunction with miglustat in clinical trials. Immune-mediated reactions have been reported with alglucosidase alfa in patients who had high IgG antibody titres, including severe cutaneous reactions and nephrotic syndrome.

A potential class effect cannot be excluded and patients should be monitored for signs and symptoms of systemic immune-mediated reactions, including periodic urinalysis, while receiving cipaglucosidase alfa/miglustat. If immune-mediated reactions occur, discontinuation of the administration of cipaglucosidase alfa should be considered and appropriate medical treatment initiated. The risks and benefits of re-administering cipaglucosidase alfa following an immune-mediated reaction should be considered.

Patient alert card

All prescribers of cipaglucosidase alfa/miglustat must be familiar with the physician information and management guidelines. The prescriber must discuss the risks of cipaglucosidase alfa/miglustat therapy with the patient. The patient will be provided with the patient alert card and instructed to carry the card at all times.

4.5 Interaction with other medicinal products and other forms of interaction

No drug-drug interaction studies have been conducted using cipaglucosidase alfa alone or in combination with miglustat. Because it is a recombinant human protein, cipaglucosidase alfa is an unlikely candidate for cytochrome P450 mediated drug-drug interactions.

Miglustat is known to have a direct effect on the enzymatic function of major disaccharidases of the intestinal epithelium. Specifically, miglustat inhibits disaccharidases with alpha-glycosidic linkages including sucrase, maltase, and isomaltase. The strength of potential interactions can immediately interfere with digestive activity of sucrose, maltose and isomaltose leading to maldigestion, osmotic influx of water, increased fermentation, and production of irritating metabolites. Diarrhoea, abdominal pain, and abdominal distension may be symptoms of the inhibitory activity of miglustat on intestinal disaccharides. Therefore, fasting is recommended when taking miglustat to minimise gastrointestinal events (see section 4.2).

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

There is limited experience in humans with cipaglucosidase alfa and/or miglustat. It is advised that female patients of child-bearing potential should maintain reliable contraceptive methods while taking both medicines.

Pregnancy

There are no adequate or well-controlled studies with cipaglucosidase alfa and/or miglustat use in pregnant women. In non-clinical studies, cardiovascular variations and malformations were reported with miglustat and miglustat used with cipaglucosidase alfa in rabbits. The potential risk for humans is unknown. Miglustat crosses the placenta. Cipaglucosidase alfa and miglustat should not be used during pregnancy (see section 5.3).

Breast-feeding

Cipaglucosidase alfa and miglustat are excreted in breast milk based on non-clinical study in animals. Because there are no data available on effects in neonates exposed to cipaglucosidase alfa via breast milk, cipaglucosidase alfa and miglustat should not be used in women who are breastfeeding.

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). No effect on sperm concentration, motility, or morphology was seen in 7 healthy adult men who received miglustat 100 mg, orally, twice daily for 6 weeks. Studies in the rat have shown that miglustat adversely affects sperm parameters (motility and morphology), and thereby reducing fertility.

Contraceptive measures should be used by women of child-bearing potential. Male patients should maintain reliable contraceptive methods while on treatment with cipaglucosidase alfa in conjunction with miglustat.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Miglustat and/or cipaglucosidase alfa may have minor influence on the ability to drive and use machines. Patients suffering from dizziness should not drive or use machines.

4.8 Undesirable Effects

Summary of the safety profile

Safety data from the use of cipaglucosidase alfa in conjunction with miglustat were available for 151 subjects treated with cipaglucosidase alfa-miglustat across three clinical trials: an open-label phase 1/2 study ATB200-02, n = 29; phase 3 study ATB200-03 [PROPEL], n = 81; an open-label extension study ATB200-07, n = 37 subjects who completed PROPEL and were switched from alglucosidase alfa. The total median duration of exposure for the 3 studies was 21.1 months, with 120 subjects having at least 12 months exposure to cipaglucosidase alfa-miglustat. The majority of subjects (117 [77.5%]) were ERT-experienced, with a mean ERT treatment duration of 7.7 years.

The most frequently reported adverse drug reactions (ADRs) in ≥ 10% in cipaglucosidase alfa-miglustat treated subjects in all 3 studies were headache (35.1%), arthralgia (28.5%), myalgia (23.2%), diarrhoea (20.5%), nausea (19.9%), abdominal pain (18.5%), fatigue (18.5%), muscle spasms (13.2%), pyrexia (12.6%), and dizziness (11.9%).

Tabulated summary of undesirable effects

The corresponding frequency category for each treatment related adverse events is based on the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000). Due to the small patient population, a treatment related adverse event reported in 1 subject is classified as common. Adverse drug reactions were based on pooled analyses for the clinical studies (Table 1) and are listed by MedDRA system organ class.

Table 1. Adverse drug reactions in subjects from clinical studies ATB200-02, ATB200-03, and ATB200-07 using cipaglucosidase alfa with miglustat

System Organ Class **Frequency**	**Preferred Term**
Immune system disorders	
Common	Anaphylactic reaction[6]
Uncommon	Hypersensitivity

System Organ Class Frequency	Preferred Term
Nervous system disorders	
Very common	Headache, dizziness
Common	Migraine[4], tremor, presyncope, somnolence, burning sensation, paraesthesia, dysguesia
Uncommon	Balance disorder
Cardiac disorders	
Common	Tachycardia[7]
Vascular disorders	
Common	Flushing, hypotension
Uncommon	Pallor
Respiratory, thoracic, and mediastinal disorders	
Common	Cough, dyspnoea, asthma
Uncommon	Oropharyngeal discomfort, pharyngeal oedema, wheezing
Gastrointestinal disorders	
Very common	Diarrhoea, nausea, abdominal pain[1]
Common	Vomiting, abdominal distension, flatulence, dyspepsia, constipation, abdominal discomfort, oral pain
Uncommon	Oesphageal spasm, oesphageal pain, oral discomfort, swollen tongue
Skin and subcutaneous disorders	
Common	Rash[2], urticaria[3], pruritus, hyperhidrosis
Uncommon	Skin discolouration, skin oedema
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia, myalgia, muscle spasms
Common	Muscular weakness, muscle fatigue, musculoskeletal stiffness, flank pain
General disorders and administration site conditions	
Very common	Fatigue, pyrexia
Common	Chills, pain, non-cardiac chest, asthenia, chest discomfort, infusion site swelling, malaise, peripheral swelling, feeling jittery, infusion site pain
Uncommon	Facial pain
Investigations	
Common	Blood pressure increased[5], platelet count decreased
Uncommon	Body temperature fluctuation, lymphocyte count decreased
Injury, poisoning and procedural complications	
Common	Skin abrasion

1 Abdominal pain, abdominal pain upper, and abdominal pain lower are grouped under abdominal pain.
2 Rash,rash erythematous, and rash macular are grouped under rash.
3 Urticaria, mechanical urticaria, and urticarial rash are grouped under urticaria.
4 Migraine and migraine with aura are grouped under migraine.
5 Hypertension, and blood pressure increased are grouped under blood pressure increased.

6 Anaphylaxis, anaphylactic reaction, are grouped under anaphylactic reaction. Anaphylactoid reaction is manually coded to anaphylaxis.
7 Tachycardia and sinus tachycardia are grouped under tachycardia.

Infusion-associated reactions

Study ATB200-02

Out of 2,024 infusions, there were 76 events of IARs in 11 subjects; approximately 2% of all infusions were associated with 1 or more IARs. The majority of IAR TEAEs were mild or moderate in severity. One severe IAR TEAE of pharyngeal edema was reported. Twelve IAR TEAEs reported in 3 subjects were serious: chills, cough, dyspnea, flushing, pharyngeal edema, presyncope, urticaria, and wheezing. The serious IARs did not lead to study discontinuation, except urticaria, which led to discontinuation in 1 subject. No anaphylaxis, anaphylactic reactions, life threatening or fatal IARs have been reported. All subjects with IARs (except 1 subject) responded well to premedications and continued on treatment.

Study ATB200-03

Out of 2182 infusions in the cipaglucosidase alfa/miglustat group, there were 97 events of IARs in 21 subjects. Approximately 2.7% of all infusions in cipaglucosidase alfa/miglustat group were associated with 1 or more IAR TEAE. Infusion-associated reactions occurring in at least 2 subjects exposed to cipaglucosidase alfa-miglustat included: abdominal distension, chills, pyrexia, dizziness, dysgeusia, dyspnoea, pruritus, rash, and flushing. Ten severe IAR-TEAEs were reported in 3 subjects (anaphylactic reaction, dyspnoea, flushing, chills, pruritus, and 5 events of urticaria).
One subject experienced a serious adverse reaction of anaphylactoid reaction (characterized by generalised pruritus, dyspnoea, and hypotension) during the ATB200-03 study. Two subjects receiving cipaglucosidase alfa-miglustat discontinued treatment due to infusion-associated reactions (anaphylactoid reaction and chills). Most infusion-associated reactions were mild or moderate in severity, transient in nature and none were assessed as life-threatening or fatal. Most subjects who experienced infusion-associated reactions were able to continue treatment with cipaglucosidase alfa-miglustat.

Study ATB200-07

Two subjects experienced serious IARs leading to study drug discontinuation. One subject experienced 2 severe IAR-TEAEs of urticaria and hypotension and another subject experienced an anaphylactic reaction, characterised by rash, angioedema and dyspnoea. Both events were assessed as serious, related to cipaglucosidase alfa-miglustat, and resolved with administration of antihistamines and cessation of infusion.

<u>Immunogenicity</u>

In study ATB200-02, antidrug antibodies (ADAs) were observed in all patients in the course of the treatment with variable titres; some were neutralising.
Analyses based on limited interim data indicate that immunogenicity did not appear to impact cipaglucosidase alfa pharmacokinetics, safety (IARs), or efficacy.

<u>Immune-mediated reactions</u>

No events consistent with immune-mediated reactions were identified in patients treated with cipaglucosidase alfa in conjunction with miglustat in clinical trials. Immune-mediated reactions have been reported with alglucosidase alfa, including severe cutaneous reactions and nephrotic syndrome (in subjects who had high IgG antibody titres (≥102, 400), and a potential class effect cannot be excluded (see section 4.4).

4.9 Overdose

There is no experience with overdose of cipaglucosidase alfa. Overdose has not been reported for use with miglustat in this therapy.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Cipaglucosidase alfa: Pharmacotherapeutic group: not yet assigned, ATC code: not yet assigned

Miglustat: Pharmacotherapeutic group: not yet assigned, ATC code: not yet assigned

Mechanism of action

The Pompe disease phenotype is characterized by accumulation of internal vesicular compartments caused by defective autophagy. Cipaglucosidase alfa is a recombinant lysosomal acid alpha glucosidase providing an exogenous acid alpha-glucosidase enzyme (rhGAA) source. Cipaglucosidase alfa has two molecular mechanisms as a modulator of autophagy: (1) degrading glycogen to glucose by hydrolysis of glycosidic bonds, and (2) reversing or improving pathogenic processes by alleviating lysosomal proliferation and a series of extra-lysosomal events including autophagy.

Cipaglucosidase alfa contains 10-fold higher amount of bis-phosphorylated N-glycans (bis-M6P) than alglucosidase alfa. Bis-M6P N-glycans have high affinity for the cation-independent mannose 6-phosphate receptor (CI-MPR).

Miglustat binds selectively with cipaglucosidase alfa; thereby stabilizes the conformation of cipaglucosidase alfa and minimizes the loss of enzyme activity and protects cipaglucosidase alfa in the circulation at the unfavorable physiological pH of blood.

Pharmacodynamic effects

Pharmacodynamic assessments were performed for plasma GAA activity, total GAA protein concentration, plasma miglustat concentrations, urine Hex4, and serum creatine kinase (CK). GAA activity levels trended in a very similar manner to total GAA protein pharmacokinetics results. Plasma GAA activity increased in a dose-dependent manner similar to total GAA protein concentrations.

Urine Hex4 levels decreased from baseline starting on the administration of the first dose of study medication and continued to decrease until the end of treatment. Like urine Hex4 levels, overall CK values decreased from baseline until the end of treatment. Decreases in urine Hex4 and serum CK levels were observed in all patients, with the largest decrease in ERT-naïve subjects.

Clinical efficacy and safety

Clinical study ATB200-02

This clinical study was conducted in 4 different cohorts: cohort 1 = ambulatory ERT-experienced with alglucosidase (≥ 2 to ≤ 6 years at every-other-week [QOW]) patients; cohort 2 = non ambulatory (wheelchair) ERT experienced (≥ 2 years) patients; cohort 3 = ambulatory naïve (≥ 18 years) patients; cohort 4 = ambulatory ERT-experienced (> 7 years) patients. Ambulatory patients entering the study had to be able to walk 200 to 500 meters (m) on the 6-minute walk distance (6MWD) and the upright forced vital capacity (FVC) must be 30% to 80% of predicted normal value.

Motor function

Improvements in motor function were observed in ambulatory subjects across cohorts in both ERT experience and naïve patients, as measured by the 6-minute walk distance (6MWD). At baseline, the mean 6MWD for all ambulatory subjects (cohorts 1, 3, and 4) was 394.2 m and all ERT experienced

ambulatory subjects (cohorts 1 and 4) was 393.5 m. Mean changes and percent changes from baseline to month 12 were 39.9 m and 10.1% for all ambulatory subjects and 33.5 m and 8.7% for ERT experienced ambulatory subjects. A total of 13 of 29 subjects experienced improvement from baseline to month 12 in both 6MWD and percent predicted sitting FVC.

Table 2. Summary of 6-minute walk distance (6MWD) in ambulatory patients

6-minute walk distance test (6MWD) meters	Ambulatory (cohorts 1, 3, 4)	Ambulatory Naïve (cohort 3)	Ambulatory ERT-experienced (cohorts 1, 4)
Pre-treatment baseline			
N	22	6	16
Median	359.2	395.2	394.5
Mean (SD)	394.2 (107.59)	396 (75.20)	393.5 (119.66)
(95% confidence interval)	(346, 442)	(317, 475)	(330, 457)
Change from baseline to Week 52			
N	22	6	16
Median	27.4	55.6	20.6
Mean (SD)	39.9 (45.69)	57 (29.96)	33.5 (49.62)
(95% confidence interval)	(20, 60)	(26, 88)	(7, 60)

Pulmonary function

Improved pulmonary function test (PFT) for ERT-naïve subjects (cohort 3) and stable (or improved PFT for ERT-experienced subjects were observed regardless of ambulatory status, as measured by percent predicted sitting forced vital capacity (FVC).

Table 3. Summary of sitting FVC in ambulatory patients

Percent predicted sitting FVC (%)	Ambulatory (cohorts 1, 3, 4)	Ambulatory ERT-experienced (cohort 4)	Ambulatory ERT-experienced (cohorts 1, 4)
Pre-treatment baseline			
N	22	6	16
Median	56.0	66.0	56.0
Mean (SD)	57 (17.45)	65.3 (21.06)	57.4 (17.42)
(95% confidence interval)	(49, 65)	(43, 87)	(48, 67)
Change from baseline to Week 52			
N	22	6	16
Median	0.5	1.5	-1.5
Mean (SD)	03 (6.86)	1.0 (5.73)	-1.3 (5.95)
(95% confidence interval)	(-3, 3)	(-5, 7)	(-4, 2)

Note: Pulmonary function tests were summarized at baseline, every 3 months in stage 3 and every 6 months in stage 4 for all ambulatory subjects and for non-ambulatory subjects without invasive ventilatory support. Higher values indicate improving vital capacity. ERT (alglucosidase alfa) for ≥ 2 years to ≤ 6 years (cohort 1) and ≥ 7 years (cohort 4) prior to enrolment.

Muscle strength test score

Improvements in muscle strength were observed in all tested body parts of both ambulatory and non-ambulatory subjects in stages 3 and 4, as measured by the manual muscle test (MMT).

Table 4. Summary of total score of manual muscle test in ambulatory and non-ambulatory patients

Manual muscle test (MMT) total score*	Ambulatory (cohorts 1, 3, 4)	Ambulatory ERT-experienced (cohorts 1, 4) †	Non-ambulatory ERT-experienced (cohort 2)‡
Pre-treatment baseline			
N	20	15	5
Median	66.5	65.0	16.0
Mean (SD)	65.6 (5.88)	65.1 (6.46)	18.4 (13.96)
(95% confidence interval)	(63, 68)	(61, 69)	(1, 36)
Change from baseline to Week 52			
N	20	15	4
Median	4.0	4.0	2.0
Mean	3.9 (3.51)	4.3 (3.20)	1.3 (3.40)
(95% confidence interval)	(2, 5)	(3, 6)	(-4, 7)

* MMT total score ranges from 0 to 80 based on all 16 muscle groups, which are right/left shoulder abduction, right/left shoulder adduction, right/left elbow flexion, right/left elbow extension, right/left hip flexion, right/left hip abduction, right/left knee flexion, and right/left knee extension. For non-ambulatory patients, MMT total score was based on the upper body parts and ranges from 0 to 40. Higher scores indicate less disease impact on muscle functions.
The MMTs were summarized at baseline, every 3 months in stage 3 and every 6 months in stage 4 for all subjects.
The MMT score at each visit is calculated only if the subject has the corresponding test scores for all applicable muscle groups.

† ERT (alglucosidase alfa) for ≥ 2 to ≤ 6 years (cohort 1) and ≥ 7 years (cohort 4) prior to enrolment

‡ ERT (alglucosidase alfa) for ≥ 2 years prior to enrolment

Fatigue

All subjects were significantly impacted by fatigue at baseline and showed improvements in fatigue severity scale (FSS) total score from baseline to week 52 in stage 3; improvements were sustained through 24 months for cohorts 1 through 3.

Table 5. Summary of fatigue severity scale total score in ambulatory and non-ambulatory patients

Fatigue severity scale (FSS) total score*	Ambulatory (cohorts 1, 3, 4)	Ambulatory ERT-experienced (cohorts 1, 4)	Non-ambulatory ERT-experienced (cohort 2)
Pre-treatment baseline			
N	21	15	6
Median	49.0	52.0	50.5
Mean (SD)	47.8 (12.00)	49.9 (11.00)	46.8 (13.47)
(95% confidence interval)	(42, 53)	(44, 56)	(33, 61)
Change from baseline to Week 52			
N	21	15	5
Median	-3.0	-2.0	-13.0
Mean (SD)	-3.9 (9.64)	-2.9 (10.55)	-9.2 (11.37)
(95% confidence interval)	(-8, 0)	(-9, 3)	(-23, 5)

* Fatigue severity scale (FSS) scores were summarized at baseline, every 3 months in stage 3 and every 6 months in stage 4 for all subjects. FSS consists of 9 questions, each scored on a scale from 1 (“completely disagree”) to 7 (“completely agree”). The total score ranges from 9 to 63, with higher values representing higher level of fatigue due to the disease condition.

ATB200-03 Clinical Study

A 52-week phase 3 randomized, double-blind, active-controlled, international, multi-center clinical study was conducted in adult subjects (≥ 18 years) diagnosed with Pompe Disease. Subjects were

randomized 2:1 to receive cipaglucosidase alfa/miglustat or alglucosidase alfa/placebo every other week for 52 weeks. The efficacy population excluding outlier included a total of 122 subjects of which 95 had received prior Enzyme Replacement Therapy (ERT) with alglucosidase alfa (ERT-experienced) and 27 had never received ERT (ERT-naïve).

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

Pulmonary Function

Sitting Percent-predicted Forced Vital Capacity (FVC) at 52 weeks

Subjects treated with cipaglucosidase alfa/miglustat showed less of a decline in FVC from baseline (-0.9%) as compared with subjects treated with alglucosidase alfa/placebo (-4.0%), indicating a treatment effect of 3.0% (p = 0.023) (Table 6).

The ERT-experienced subjects treated with cipaglucosidase alfa/miglustat showed no decline in FVC from baseline (0.1%) as compared with subjects treated with alglucosidase alfa/placebo (-4.0%) indicating a treatment effect of 4.1% (p = 0.006).

Table 6. Summary of Percent Predicted FVC in the Overall Adult Population at 52 Weeks

Sitting Percent Predicted FVC	**Cipaglucosidase alfa/miglustat**	**alglucosidase alfa/placebo**
Baseline n Median Mean (SD)	 n = 85 70.0 70.7 (19.6)	 n = 37 71.0 69.7 (21.5)
Change from baseline at Week 52 n Median Mean (SD) (95% CI)	 n = 84 -1.0 -0.93 (6.2) (-2.3, 0.4)	 n = 37 -3.0 -3.95 (4.9) (-5.6, -2.3)
Change to Week 52 Diff. of means (SE) (95% CI of difference) 2-sided p value	 3.0 (1.2) (0.7, 5.3) p = 0.023	

SD: standard deviation; SE: standard error; CI: confidence interval; Diff.: difference

Motor Function

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

Subjects treated with cipaglucosidase alfa-miglustat walked on average 20.8 meters farther from baseline as compared to those treated with alglucosidase alfa-placebo that walked 7.2 meters farther from baseline (p = 0.071) (Table 7).

The ERT-experienced subjects treated with cipaglucosidase alfa-miglustat had a mean improvement in walk distance from baseline of 16.9 meters as compared to a mean of 0 meters for alglucosidase alfa-placebo (p = 0.047).

Table 7. Summary of 6MWD in Overall Adult Population at 52 Weeks

6MWD (meters)	Cipaglucosidase alfa-miglustat	alglucosidase alfa-placebo
Baseline n Median Mean (SD)	 n = 85 359.5 357.9 (111.8)	 n = 37 365.5 351.0 (121.3)
Change from baseline at Week 52 n Median Mean (SD) (95% CI)	 n = 85 12.5 20.8 (42.8) (11.6, 30.0)	 n = 37 1.4 7.2 (40.3) (-6.2, 20.7)
Change to Week 52 Diff. of means (SE) (95% CI) 2-sided p value	 13.5 (8.3) (-2.8, 29.9) p = 0.071	

SD: standard deviation; SE: standard error; CI: confidence interval; Diff.: difference

5.2 Pharmacokinetic properties

Following administration with 20 mg/kg cipaglucosidase alfa with 260 mg miglustat, total GAA protein partial AUCtmax-24h increased by 44% relative to 20 mg/kg cipaglucosidase alfa alone, indicating binding and stabilization by miglustat during the distribution phase of elimination. The distribution half-life was also increased following usage of both cipaglucosidase alfa and miglustat by 47%. Correspondingly, plasma clearance decreased by 27%, suggesting enhanced uptake into tissues.

Table 8. Mean (CV%) cipaglucosidase PK summary at clinical dose treatment group

Treatment Group (n)	Co-hort	C_{max} (mcg/mL)	AUC_{0-t} (mcg h/mL)	$AUC_{tmax-24h}$ (mcg h/mL)	$AUC_{0-\infty}$ (mcg h/mL)	$t_{½\alpha}$ (h)	CLT (L/h)
Cipa 20 mg/kg alone (n =11)	1	325 (13.5)	1405 (16.2)	837 (19.4)	1410 (15.9)	1.5 (8.7)	1.26 (17.8)
Cipa 20 mg/kg + miglustat 260 mg (n = 11)	1	345 (18.5)	1801 (19.9)	1203 (23.4)	1812 (20.8)	2.1 (16.1)	0.991 (22.3)
Cipa 20 mg/kg + miglustat 260 mg (n = 6)	3	323 (12.8)	1772 (17.3)	1153 (18.7)	1774 (17.4)	2.2 (9.1)	0.769 (25.5)

Abbreviations: Cipa = cipaglucosidase alfa; AUC_{0-t} = area under the curve from 0 to t; $AUC_{0-\infty}$ = area under the curve from 0 to infinity; C_{max} = maximum observed plasma concentration; n = number of subjects; $t_{½\ \alpha}$ = half-life alpha; $AUC_{tmax-24\ h}$ = area under the curve time to reach the maximum observed plasma concentration to 24 hours
cohort 1: ambulatory ERT-experienced adults with LOPD; cohort 3: ambulatory ERT-naïve adults with LOPD

During the terminal phase time-points of 12- and 24-hours post start of cipaglucosidase alfa infusion, statistically significant increases in total GAA protein are observed following combination administration with 130 mg and 260 mg miglustat relative to 20 mg/kg cipaglucosidase alfa alone. At 12-hours post dose, the differences were highly significant ($p < 0.01$ or 0.001) for 260 mg miglustat combination administration. Plasma GAA activity levels also had highly statistically significant increases at 12- and 24-hours following the administration of miglustat in conjunction with 130 mg and 260 mg miglustat relative to 20 mg/kg cipaglucosidase alfa alone.

Miglustat is largely unmetabolized with < 5% of a radiolabeled dose recovered as glucuronides. Miglustat demonstrated dose proportional kinetics. The rate of absorption (t_{max}) of miglustat was approximately 3 hours. At the clinical dose, 260 mg, plasma miglustat attained a C_{max} of

approximately 3,000 ng/mL and an $AUC_{0-\infty}$ of approximately 25,000 ng*h/mL. The terminal elimination half-life was approximately 6 hours. Oral clearance was approximately 10.5 L/h and terminal phase volume of distribution was approximately 90 L.

Special populations

Elderly

The pharmacokinetics of cipaglucosidase alfa / miglustat have not been evaluated in elderly patients.

Renal Impairment

Plasma miglustat concentrations do not accumulate following administration of orally administered 260 mg miglustat one hour before IV infusion of 20 mg/kg cipaglucosidase alfa. Therefore, dose adjustment is not required for patients with renal impairment.

Hepatic Impairment

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

Gender

There were no clinically relevant differences observed in cipaglucosidase alfa/miglustat pharmacokinetics between males and females.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity, carcinogenicity, genotoxicity, and mutagenicity.

Fertility and early embryonic development (FEE) and embryo-fetal development (EFD) studies demonstrated that the effects of the combination of cipaglucosidase alfa/miglustat were mainly related to miglustat. In the FEE study in rats, an increase in pre-implantation loss observed in the combination treatment group (400 mg/kg cipaglucosidase alfa/60 mg/kg miglustat) was considered miglustat related. Additionally, in the EFD study in the New Zealand rabbit in the combination group (175 mg/kg cipaglucosidase alfa / 25 mg/kg miglustat), maternal toxicity was evident based on miglustat-related decreased body weight gain and reduced food consumption. Significant safety findings were observed including an increase in the total number of fetal malformations of the heart and blood vessels when compared to controls. Fetal malformations were attributed to the administration of cipaglucosidase alfa in conjunction with miglustat, as both the frequency and variety of malformations observed were greater than in the control group of miglustat alone. It should be noted however that the dose levels in the clinic are largely supported by safety margins with an every-other-week (QOW) clinical dosing regimen compared to FEE and EED toxicity studies that were performed with an every-other-day (QOD) dosing.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

Miglustat
Capsule contents:

- Pregelatinised starch (maize)

- Magnesium stearate (E470b)
- Microcrystalline cellulose (E460i)
- Sucralose (E955)
- Colloidal silicon dioxide

Capsule shell:

- Gelatin
- Titanium dioxide (E171)
- Black iron oxide (E172)

Edible Printing ink:

- Black iron oxide (E172)
- Shellac (E904)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened container

Cipaglucosidase alfa in a sealed lyophilised 20 mL vial: 24 months
Miglustat capsules in a 40 cc bottle with cap: 36 months

Reconstitution and ready for infusion

Cipaglucosidase alfa

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

From a microbiological point of view, cipaglucosidase alfa in the IV bag should be administered immediately. In-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C unless reconstitution / dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Cipaglucosidase alfa:

Store in a refrigerator (2°C to 8°C).
Do not freeze.
Store in the original package in order to protect from light.

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

Miglustat:

This product does not require special storage conditions.
Keep this medicine out of the sight and reach of children.

6.5 Nature and contents of container

Cipaglucosidase alfa: Lyophilized cipaglucosidase alfa, 105 mg/vial
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.

6.6 Special precautions for disposal and other handling

Preparation before the Infusion

Use aseptic technique.

Each vial of cipaglucosidase alfa is for single-use only.

Calculating the dose

Determine the number of cipagluocosidase alfa 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 subject 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.
- Extraction volume per vial is 7.0 mL. Remove 7.0 mL from each of the 12 vials; 0.38 vial times 7.0 ml= 2.66 ml rounded to 2.7 mL from the 13th vial.

Items needed for Reconstitution and Dilution

- Cipaglucosidase alfa> 105 mg vials
- Sterile water for injection at room temperature of 68°F to 77°F (20°C to 25°C)
- Sodium chloride 9 mg/mL (0.9%) for Injection at room temperature of 68°F to 77°F (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**

  Do not use filter needles that reduce particulate during preparation.

Activities before Reconstitution

Cipaglucosidase alfa vials should be removed from the refrigerator (36° to 46°F; 2° to 8°C) and allowed to come to room temperature (ie, approximately 30 minutes at 68°F to 77°F (20°C to 25°C).

Do not use if the vial has fluid, contents discoloured is chipped, cracked, closure damaged or button of overseal removed.

Reconstituting the Lyophilized Cake/Powder

1. Reconstitute each vial by slowly adding 7.2 mL sterile water for injection dropwise down the inside of the vial with rather than directly onto the lyophilized cake or powder. Avoid forceful impact of sterile water for injection on the lyophilized powder and avoid foaming.
2. Tilt and roll each vial gently to dissolve the powder or cake. Do not invert, swirl, or shake. Reconstitution of the lyophilized cake or powder typically takes 2 minutes.
3. Perform an inspection of the reconstituted vials for particulate matter and discoloration. The reconstituted volume appears as a colorless to pale yellow solution, and may appear almost free of particles but may contain white to translucent particles. If upon immediate inspection foreign matter are observed or if the solution is discolored, do not use.

Each reconstituted vial has a concentration of 15 mg/mL with an extractable volume of 7.0 mL.

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

Dilution and Preparation of the Infusion Bag

1. Remove airspace within the infusion bag. Remove an equal volume of sodium chloride 9 mg/mL (0.9%) solution for injection that will be replaced by the total volume (mL) of reconstituted cipaglucosidase alfa.
2. Slowly withdraw the reconstituted solution from the vials until the patient's dose is obtained. Avoiding foaming in the syringe.
3. Slowly inject the reconstituted cipaglucosidase alfa directly into the sodium chloride 9 mg/mL (0.9%) solution for injection bag. Do not add directly into the air space that may remain within the infusion bag.
4. Gently invert or massage the bag to mix the diluted solution. 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

Infusion can be administered in all sites of patient care including at home, in-clinic, and in-hospital after comprehensive evaluation of infusion-associated allergic reaction risks under the supervision of a healthcare professional (see sections 4.3 and 4.4).

If it is not possible start the infusion following dilution, the reconstituted and diluted solution is stable for up to 30 hours refrigerated at 36°F to 46°F (2°C to 8°C). While storage at room temperature is not recommended, refer to the in-use stability storage conditions. Do not freeze or shake.

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

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

An intravenous administration set should be used with an inline low protein binding 0.2-micron filter. If the intravenous line blocks during infusion, change the filter.

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

Disposal

Miglustat and cipaglucosidase alfa

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

7. SCIENTIFIC OPINION HOLDER

Amicus Therapeutics Europe Limited
Block 1, Blanchardstown Corporate Park
Ballycoolin Road
Blanchardstown, Dublin

D15 AKK1
Ireland
e-mail: info@amicusrx.co.uk

8. EAMS NUMBER

50636/0001

9. DATE OF SCIENTIFIC OPINION

04/06/2021

Additional Information

Healthcare professionals will be provided with the following documents to give to patients to help minimise the risk of infusion-related adverse reactions:

Treatment protocol – Information for patients

Patient information brochure, directed at patients, containing key information on infusion related with cipaglucosidase alfa and hypersensitivity side effects with cipaglucosidase alfa and miglustat.

Patient Alert Card

After a patient signs the ***EAMS Informed Consent Form***, a ***Patient Alert Card***, a wallet size card, is given to the patient. Each patient should be advised to always carry the Patient Alert Card and for at least 12 months after completing treatment. The patient should be instructed to show it at all medical visits and to other healthcare professionals that are treating the patient.

- Please direct the patient to complete all relevant sections of the card, including contact information for the prescriber, patient, and any caregiver who plays a role in helping the patient. This card can be especially helpful in visits to emergency healthcare facilities, where the patient may be unknown.
- Please take a moment to ensure that the patient understands how to use the patient alert card. Inform that it contains summary information about treatment and how to appropriately manage adverse reactions. A physician or nurse should emphasise the importance of completing the card and carrying it while on treatment.
- Most importantly, each patient should be reminded that if he or she does experience an adverse reaction, he or she should seek medical attention immediately and undergo prompt treatment.

EAMS registration

To register a patient with the EAMS, healthcare professionals will refer to the below contact information.

Contact information

Contact details for reporting Adverse Events/Special Situations

YellowCard: https://yellowcard.mhra.gov.uk alternatively you can call Freephone 0808 100 3352 (available between 10am-2pm Monday – Friday), or

Email: drugsafety@amicusrx.com

Contact details for EAMS programme and Medical Information

Marlow, United Kingdom telephone: 01753 888567
Email: info@amicusrx.co.uk