SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Opfolda 65 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 65 mg of miglustat.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Hard capsule

Size 2 hard capsule (6.35x18.0 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

Opfolda (miglustat) is an enzyme stabiliser of cipaglucosidase alfa long-term enzyme replacement therapy in adults with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency).

4.2 Posology and method of administration

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

Miglustat 65 mg hard capsules must be used in combination with cipaglucosidase alfa. The summary of product characteristics (SmPC) for cipaglucosidase alfa should be consulted before taking miglustat.

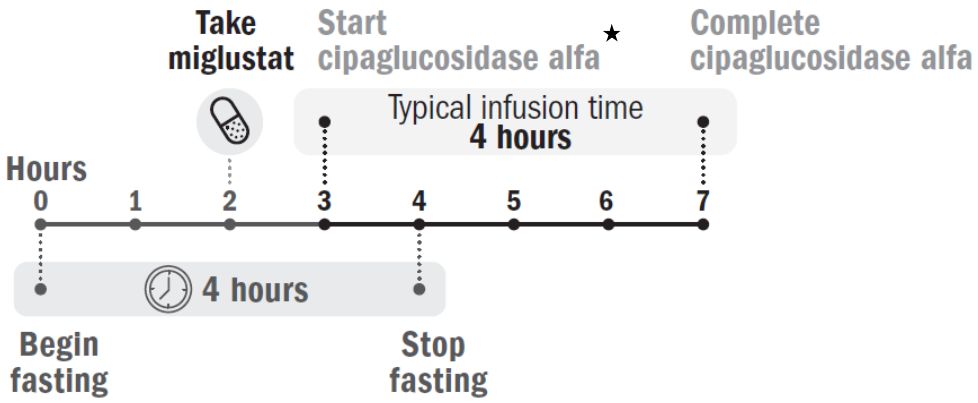
Posology

The recommended dose is to be taken every other week in adults aged 18 years and older and is based on body weight:

- For patients weighing ≥ 50 kg, the recommended dose is 260 mg (4 capsules of 65 mg).
- For patients weighing ≥ 40 kg to < 50 kg, the recommended dose is 195 mg (3 capsules of 65 mg).

Miglustat 65 mg hard capsules should be taken orally approximately 1 hour but no more than 3 hours before the start of the cipaglucosidase alfa infusion.

Figure 1. Dose timeline



★ Miglustat 65 mg hard capsules should be taken approximately 1 hour but no more than 3 hours before the start of the cipaglucosidase alfa infusion.

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 miglustat 65 mg hard capsules in combination with cipaglucosidase alfa treatment should be considered. Both medicinal products should either be continued or discontinued.

Missed dose

If the miglustat dose is missed, treatment should occur as soon as possible. If it is not taken, do not start the cipaglucosidase alfa infusion. Cipaglucosidase alfa infusion can start 1 hour after miglustat is taken.

Special populations

Renal and hepatic impairment

The safety and efficacy of miglustat in combination with cipaglucosidase alfa 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 or hepatic impairment.

Elderly

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

Paediatric population

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

Method of administration

Miglustat is for oral use.

Miglustat 65 mg hard capsule has a crimp to prevent opening the capsule shells and should be swallowed whole and taken on an empty stomach.

Patients should fast 2 hours before and 2 hours after taking miglustat 65 mg hard capsules (see section 5.2). During this 4-hour fasting period, water, fat-free (skimmed) cow's milk, and tea or coffee with no cream, sugars, or sweeteners can be consumed. The patient can resume normal eating and drinking 2 hours after taking miglustat.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Contraindication to cipaglucosidase alfa.

4.4 Special warnings and precautions for use

Miglustat 65 mg hard capsules must be used in combination with cipaglucosidase alfa. Because of this, the summary of product characteristics (SmPC) for cipaglucosidase alfa should be consulted in relation to its safety profile before taking miglustat.

Adverse drug reactions may occur upon the use of miglustat in combination with cipaglucosidase alfa (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed related to the use of miglustat.

Food interaction

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. Patients should fast for 2 hours before and for 2 hours after taking miglustat.

4.6 Fertility, pregnancy, and lactation

Contraception in females

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

Pregnancy

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

Breast-feeding

It is not known if miglustat and cipaglucosidase alfa are secreted in human breast milk (see section 5.3). Available pharmacodynamic/toxicological data in animals have shown secretion of miglustat and excretion of cipaglucosidase alfa in milk. A risk to new-borns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from miglustat in combination with cipaglucosidase alfa 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 miglustat in combination with cipaglucosidase alfa therapy on fertility.

No effects on sperm concentration, motility, or morphology were seen in 7 healthy adult men who received miglustat 100 mg, orally, twice daily for 6 weeks.

In male rats, no effect on spermatogenesis was observed following administration of miglustat in combination with cipaglucosidase alfa or miglustat alone. However, preclinical data from a study in rats using another miglustat product have shown that miglustat adversely affects sperm parameters (motility and morphology), thereby reducing fertility (see section 5.3).

In female rats, increase in pre-implantation loss was noted with miglustat in combination with cipaglucosidase alfa and with miglustat alone (see section 5.3).

4.7 Effects on ability to drive and use machines

Miglustat has no or negligible influence on the ability to drive or to use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reaction only attributable to miglustat 65 mg was constipation (1.3%).

Tabulated list of adverse reactions

The assessment of adverse reactions was informed by subjects treated with miglustat in combination with cipaglucosidase alfa therapy from the pooled safety analysis across the 3 clinical trials. The total mean duration of exposure was 28.0 months.

Adverse reactions are listed by MedDRA system organ class in Table 1.

The corresponding frequency categories are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10 000 to < 1/1000), very rare (< 1/10 000), and not known (cannot be estimated from available data).

Table 1: Summary of adverse reactions of miglustat-treated patients

System organ class (SOC)	Frequency	Adverse reaction (preferred term)
Immune system disorders	Common	Anaphylactic reaction[7]
	Uncommon	Hypersensitivity
Nervous system disorders	Very common	Headache
	Common	Tremor, dysgeusia, paraesthesia
	Uncommon	Balance disorder, migraine[4]
Cardiac disorders	Common	Tachycardia[6]
	Common	Hypotension
	Uncommon	Pallor
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
	Uncommon	Asthma
Gastrointestinal disorders	Common	Diarrhoea, nausea, abdominal pain[1], flatulence, abdominal distension, vomiting, constipation[†]
	Uncommon	Abdominal discomfort[†], oesophageal spasm, oral pain
Skin and subcutaneous tissue disorder	Common	Urticaria[3], rash[2], pruritus, hyperhidrosis
	Uncommon	Skin discolouration
Musculoskeletal and connective tissue disorders	Common	Muscle spasms, myalgia, arthralgia, muscular weakness
	Uncommon	Flank pain, muscle fatigue, musculoskeletal stiffness
General disorders and administration site conditions	Common	Fatigue, pyrexia, chills, peripheral swelling
	Uncommon	Asthenia, facial pain, feeling jittery[†], non-cardiac chest pain

System organ class (SOC)	Frequency	Adverse reaction (preferred term)
Investigations	Common	Blood pressure increased[5]
	Uncommon	Lymphocyte count decreased, platelet count decreased[†]

† Reported with miglustat only

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

[2] Rash and rash erythematous are grouped under rash.

[3] Urticaria, urticaria rash, and mechanical urticaria are grouped under urticaria.

[4] Migraine and migraine with aura are grouped under migraine.

[5] Hypertension and blood pressure increased are grouped under blood pressure increased.

[6] Tachycardia and sinus tachycardia are grouped under tachycardia.

[7] Anaphylaxis, anaphylactic reaction, and anaphylactoid reaction are grouped under anaphylactic reaction.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Yellow Card Scheme

Website: at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Leukopenia, granulocytopenia, neutropenia, dizziness, and paraesthesia have been observed in human immunodeficiency virus (HIV) patients receiving miglustat at a dosage of 800 mg/day or higher.

Management

In the event of an overdose, supportive medical care should be provided immediately. Full blood counts should be monitored for reduced white cells.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products, various alimentary tract and metabolism products. ATC Code: A16AX06

Mechanism of action

Miglustat is a pharmacokinetic enzyme stabiliser of cipaglucosidase alfa.

Miglustat binds selectively with cipaglucosidase alfa in the blood during infusion; thereby stabilising the conformation of cipaglucosidase alfa and minimising the loss of enzyme activity while in circulation. This selective binding between cipaglucosidase alfa and miglustat is transient with disassociation occurring in the lysosome. Miglustat alone has no effect on glycogen reduction.

Paediatric population

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

5.2 Pharmacokinetic properties

Absorption

The rate of absorption (t_{max}) of miglustat was approximately 2 to 3 hours. At the clinical dose, 260 mg, plasma miglustat attained a C_{max} of approximately 3000 ng/mL and an $AUC_{0-\infty}$ of approximately 25,000 ng h/mL.

Effect of food

A significant food effect was observed and resulted in a decreased C_{max} by 36% and delayed absorption by approximately 2 hours (see section 4.2).

Metabolism

Miglustat is largely unmetabolised with < 5% of a radiolabeled dose recovered as glucuronides.

Miglustat is not a substrate of OAT1, OAT3, OATP1B1, OATP1B3, MATE1, MATE2-K, BCRP, or BSEP. Miglustat is a weak substrate of P-glycoprotein (P-gp) and a substrate of uptake transporters OCT1 (expressed in the liver) and OCT2 (expressed in the kidney). As miglustat is largely renally excreted unmetabolised, OCT1-inhibitors are not expected to result in a clinically meaningful interaction. OCT2 inhibitors are not expected to have a clinically meaningful impact on the renal excretion and exposure of miglustat based on data in patients with severe renal impairment. P-glycoprotein (P-gp)-inhibitors are not expected to result in a clinically meaningful interaction with miglustat in the intestine based on fasting recommendations and the rapid absorption of miglustat (t_{max} of 2 hours).

Miglustat is not a known substrate or inhibitor of cytochrome P450 enzymes; consequently, significant interactions are unlikely with drugs that are substrates of cytochrome P450 enzymes.

Based upon in vitro transporter study, miglustat is not an inhibitor of OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3 or BSEP transporters. Clinically meaningful interactions in the intestine with P-gp and BCRP substrates and in the liver at the portal vein with OCT1, OATP1B1 and OATP1B3 are not expected based on fasting recommendations and the rapid absorption of miglustat.

Elimination

The terminal elimination half-life was approximately 6 hours for miglustat. Oral clearance was approximately 10.5 L/h and terminal phase volume of distribution was approximately 90 L.

Linearity

Miglustat demonstrated dose proportional kinetics.

Special populations

Gender, elderly, and race/ethnicity

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

Hepatic impairment

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

Renal impairment

The $AUC_{0\text{-}24hr}$ of miglustat increased by 21%, 32%, and 41% in patients with mild (creatinine clearance [CLcr] 60 to 89 mL/minute, estimated by Cockcroft-Gault), moderate (CLcr 30 to 59 mL/minute), and severe (CLcr 15 to 29 mL/minute) renal impairment, respectively, compared to patients with normal renal function. The effect of end stage renal disease on the pharmacokinetics of miglustat is unknown.

5.3 Preclinical safety data

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

Carcinomas in the large intestine of mice occurred occasionally following oral treatment with miglustat at 210, 420 and 840/500 mg/kg/day for a period of 2 years. These doses correspond to 8, 16, and 33/19 times a human dose of 200 mg three times per day. The relevance of these findings to humans taking miglustat is unknown at the substantially lower studied doses at 195 to 260 mg every other week for Pompe disease.

Reproductive and developmental toxicology

In a segment I study in male rats, there was no effect of miglustat in combination with cipaglucosidase alfa therapy or miglustat alone on spermatogenesis.

In another miglustat product study in rats, miglustat administered orally resulted in seminiferous tubule and testicular atrophy/degeneration at an exposure multiple of 2.0, at the maximum recommended human dose (MRHD) based on body surface area (mg/m^2). Also, decreased spermatogenesis with altered sperm morphology and motility and decreased fertility were observed in rats at exposure multiple of 0.6 based on body surface area. Decreased spermatogenesis was reversible in rats following 6 weeks of active substance withdrawal.

In a segment I fertility and early embryonic development study in rats, pre-implantation loss was observed in the female fertility component of the study in both miglustat alone and the combination treatment group and was considered miglustat-related. For the combination treatment, margins at the MRHD of cipaglucosidase alfa and miglustat were 27-fold and 4-fold, respectively, based on plasma AUC exposure.

In a segment II embryo-foetal development study, no adverse findings directly attributed to cipaglucosidase alfa or miglustat were observed in pregnant rats or their offspring.

In an embryo-foetal development study in rabbits, maternal effects including decreased food consumption and body weight gains were evident for both miglustat alone and the combination group The combination of cipaglucosidase alfa with

miglustat (but not cipaglucosidase alfa without miglustat) resulted in increased cardiovascular malformations (atretic pulmonary trunk, ventricular septum defect, and dilated aortic arch) in rabbits at 16-fold and 3-fold the exposure at the MRHD of cipaglucosidase alfa and miglustat, respectively, based upon a single dose, or 112-fold and 21-fold, respectively, based on cumulative dosing. However, it is not possible to exclude that the embryo-foetal adverse effects observed in the rabbits could have occurred following a single exposure to the combination. A no observed adverse effect level (NOAEL) could not be established for the combination group since only one combination dose was tested.

In a segment III pre-and post-natal development study in rats, no adverse maternal or post-natal development effects directly attributed to cipaglucosidase alfa or miglustat were observed. Evaluation of milk in rats from the combination treatment group showed secretion of miglustat and excretion of cipaglucosidase alfa in rat milk. At 2.5 hours post dose, the ratio of cipaglucosidase alfa exposure in rat milk to plasma was 0.038.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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)

Potassium hydroxide (E525)

Propylene glycol (E1520)

Shellac (E904)

Strong ammonia solution (E527)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

40 mL high density polyethylene (HDPE) bottle with 33 mm white child resistant polypropylene cap with label. Bottle opening is sealed with an induction sealed foil liner.

Bottles of 4 and 24 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Amicus Therapeutics UK Limited

One Globeside

Fieldhouse Lane

Marlow, Buckinghamshire
SL7 1HZ

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 25823/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/08/2023

10 DATE OF REVISION OF THE TEXT

03/02/2025