ANNEX I

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.

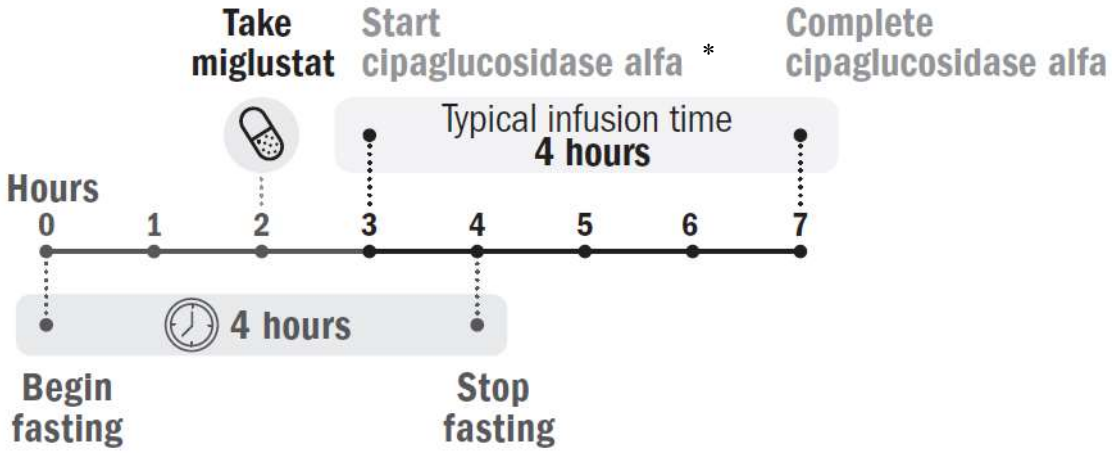
Posology

The recommended dose is to be taken orally 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 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 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

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 newborns/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 (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), and not known (cannot be estimated from available data).

Table 1: Summary of adverse reactions 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]
Vascular disorders	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

System organ class (SOC)	Frequency	Adverse reaction (preferred term)
	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
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 the national reporting system listed in Appendix V.

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 European Medicines 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 exposures 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 Europe Limited
Block 1, Blanchardstown Corporate Park

Ballycoolin Road
Blanchardstown, Dublin
D15 AKK1
Ireland
e-mail: info@amicusrx.co.uk

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1737/001
EU/1/23/1737/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 June 2023

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Manufacturing Packaging Farmaca
Neptunus 12, Heerenveen, Netherlands, 8448CN

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

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

- **Risk management plan (RMP)**

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

An updated RMP should be submitted:

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Opfolda 65 mg hard capsules
miglustat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 65 mg of miglustat.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

4 hard capsules
24 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

ATTENTION: Only use Opfolda with cipaglucosidase alfa.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Amicus Therapeutics Europe Limited
Block 1, Blanchardstown Corporate Park,
Ballycoolin Road, Blanchardstown,
Dublin D15 AKK1, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1737/001 4 hard capsules
EU/1/23/1737/002 24 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

opfolda

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL INTERMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Opfolda 65 mg hard capsules
miglustat

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

Oral use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Each hard capsule contains 65 mg of miglustat.

4 hard capsules
24 hard capsules

6. OTHER

ATTENTION: Only use Opfolda with cipaglucosidase alfa.

Amicus Therapeutics Europe Limited
Dublin D15 AKK1, Ireland

EU/1/23/1737/001 4 hard capsules
EU/1/23/1737/002 24 hard capsules

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Opfolda 65 mg hard capsules
miglustat

Read all of this leaflet carefully before you take this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Opfolda is and what it is used for

What Opfolda is
Opfolda is a medicine that is used in the treatment of late-onset Pompe disease in adults. This medicine contains the active substance 'miglustat'.

What it is used for
Opfolda is always used with another medicine called 'cipaglucosidase alfa', a type of enzyme replacement therapy (ERT). It is therefore very important that you also read the package leaflet of cipaglucosidase alfa.

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

How Opfolda works
People with Pompe disease have low levels of the enzyme acid alpha-glucosidase (GAA). This enzyme helps control levels of glycogen (a type of carbohydrate) in the body.

In Pompe disease, high levels of glycogen build up in the muscles of the body. This keeps muscles, such as the muscles that help you walk, the muscles under the lungs that help you breathe, and the heart muscle, from working properly.

Opfolda binds to cipaglucosidase alfa during treatment. This makes the shape of cipaglucosidase alfa more stable, so it can be more easily absorbed from the blood by the muscle cells that are affected by Pompe disease. When in the cells, cipaglucosidase alfa works like GAA to help break down glycogen and control its levels.

2. What you need to know before you take Opfolda

Do not use Opfolda
- If you are allergic to miglustat or any of the other ingredients of this medicine (listed in section 6).
- If you are allergic to cipaglucosidase alfa.

Warnings and precautions
Talk to your doctor, pharmacist, or nurse before taking Opfolda.

Look out for serious side effects
Opfolda is used together with cipaglucosidase alfa, a type of enzyme replacement therapy (ERT), so you should also read the package leaflet of cipaglucosidase alfa. These medicines can cause side effects that you need to tell your doctor about straight away. This includes allergic reactions. Signs of allergic reactions are listed in section 4 'Allergic reactions'. These can be severe and may happen when you are being given the medicine or during the hours after.

Tell a doctor or nurse immediately if you are experiencing infusion-related or allergic reactions or think you may be experiencing them. Inform your doctor or nurse if you have ever had any such reaction with another ERT before you are given Opfolda.

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

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

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

There is no experience with the use of Opfolda in combination with cipaglucosidase alfa during pregnancy. Your doctor will discuss with you the risks and benefits of taking these medicines.

- Do not take Opfolda or receive cipaglucosidase alfa if you are pregnant. Be sure to tell your doctor immediately if you get pregnant, think that you may be pregnant, or if you are planning to become pregnant. There may be risks to the unborn baby.
- Opfolda in combination with cipaglucosidase alfa should not be given to women who are breast-feeding. A decision will need to be made whether to stop treatment or to stop breast-feeding.

Contraception and fertility
It is advised that female patients must use reliable birth control methods prior to, while using these medicines, and for 4 weeks after stopping both medicines.

Driving and using machines
Opfolda has no or negligible influence on your ability to drive or use machines. You should also read the package leaflet of cipaglucosidase alfa, as that medicine may have an impact.

3. How to take Opfolda

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure how the medicine should be used.

How much Opfolda to take
- Opfolda (miglustat) capsules must be used with cipaglucosidase alfa. See also the package leaflet of cipaglucosidase alfa.
- If you weigh 50 kg or more, the recommended dose is 4 capsules containing each 65 mg of miglustat.
- If you weigh between 40 kg and 50 kg, the recommended dose is 3 capsules.

How often to take Opfolda

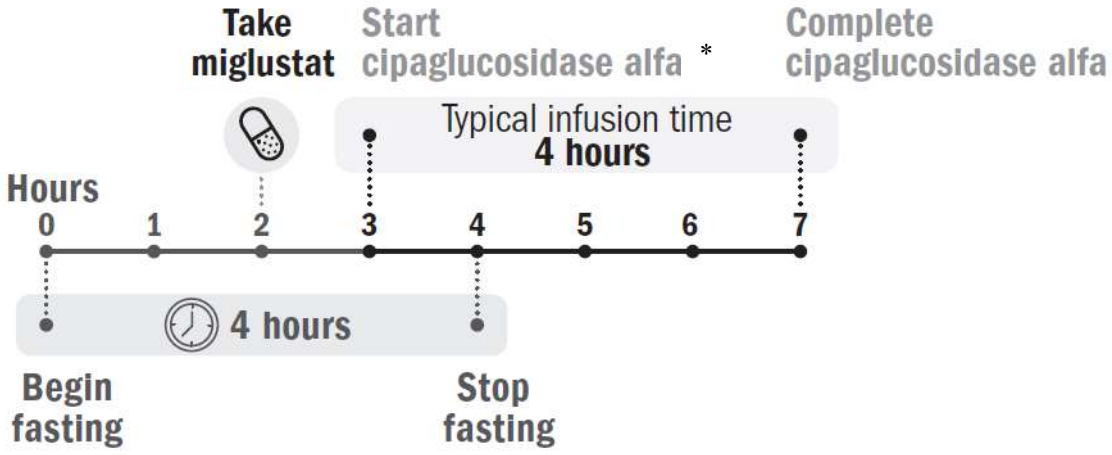
- You will receive Opfolda and cipaglucosidase alfa once every other week. Both are used on the same day.
- Take both medicines exactly as you have been told to by your doctor, see Figure 1. This is so your treatment can work as well as possible.

Opfolda with food

You must take Opfolda by mouth on an empty stomach.

- Fast for 2 hours before and 2 hours after taking this medicine.
- During this 4-hour fasting period, water, fat-free (skimmed) cow's milk, and tea or coffee can be consumed. Do not use cream, whole/semi-skimmed cow's milk, non-dairy milks, sugar, or sweeteners. You can have fat-free (skimmed) cow's milk with your tea or coffee.
- Two hours after taking Opfolda, you can resume normal eating and drinking.

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.

Switching from another enzyme replacement therapy (ERT)

If you are currently being treated with another ERT:

- Your doctor will tell you when to stop the other ERT before starting Opfolda.
- Tell your doctor when you completed your last dose.

If you take more Opfolda than you should

Tell your doctor immediately or go to the hospital if you accidentally take more capsules than you were prescribed. You may be at increased risk of experiencing side effects with this medicine (see section 4). Your doctor will provide appropriate supportive care.

If you forget to take Opfolda

If you miss a dose of Opfolda, please speak to your doctor or nurse. Contact your doctor or nurse immediately to reschedule miglustat in combination with cipaglucosidase alfa as soon as possible.

If you stop taking Opfolda

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

4. Possible side effects

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

Opfolda is used with cipaglucosidase alfa, and side effects can occur with either of these medicines.

The following side effects may occur:

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

Tell a doctor or nurse immediately if you are experiencing or think you may be experiencing allergic reactions. Inform your doctor or nurse if you have ever had any such reaction.

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

Common (may affect up to 1 in 10 people)
- Serious life-threatening allergic reaction (anaphylactic reaction)
- Tremor
- Taste disturbance
- Sensation like numbness, tingling, pins, and needles (paraesthesia)
- Rapid heartbeat
- Low blood pressure
- Shortness of breath
- Diarrhoea
- Feeling sick (nausea)
- Stomach pain
- Passing gas
- Bloating
- Vomiting
- Constipation
- Hives
- Rash
- Itchy skin
- Excessive sweating
- Painful muscle contractions
- Muscle pain
- Muscle weakness
- Joint pain
- Tiredness
- Fever
- Chills
- Swelling in the hands, feet, ankles, legs
- Rise in blood pressure

Uncommon (may affect up to 1 in 100 people)
- Allergic reaction
- Cannot hold or maintain balance
- Migraine
- Unusual paleness of the skin
- Asthma
- Uneasy stomach
- Painful contractions in gullet
- Mouth pain

- Skin discolouration
- Pain in the area between the hip and rib
- Muscle tiredness
- Muscle stiffness
- Weakness
- Pain in the cheek, gums, lips, chin
- Feeling jittery
- Pain in chest

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

5. How to store Opfolda

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle and carton after the letters "EXP". The expiry date refers to the last date of that month.

This medicine does not require any special storage conditions.

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

6. Contents of the pack and other information

What Opfolda contains
- The active substance is miglustat. Each hard capsule contains 65 mg of miglustat.

- The other ingredients are:

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)
Strong ammonia solution (E527)
Shellac (E904)

What Opfolda looks like and contents of the pack

Bottles of 4 and 24 capsules.
Not all pack sizes may be marketed.

Size 2 hard capsule with a grey opaque cap and white opaque body with “AT2221” printed in black on the body, containing white to off-white powder.

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