

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Miglustat Gen.Orph 100 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100 mg miglustat

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

White opaque cap and body, hard gelatin capsules size 4 of about 14.0 mm length.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Miglustat Gen.Orph is indicated for the oral treatment of adult patients with mild to moderate type 1 Gaucher disease. Miglustat Gen.Orph may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Therapy should be directed by physicians who are knowledgeable in the management of Gaucher disease.

Posology

Adult

The recommended starting dose for the treatment of adult patients with type 1 Gaucher disease is 100 mg three times a day.

Temporary dose reduction to 100 mg once or twice a day may be necessary in some patients because of diarrhoea.

Special populations

Paediatric population

The efficacy of Miglustat Gen.Orph in children and adolescents aged 0-17 years with type 1 Gaucher disease has not been established. No data are available.

Elderly

There is no experience with the use of Miglustat Gen.Orph in patients over the age of 70.

Renal impairment

Pharmacokinetic data indicate increased systemic exposure to miglustat in patients with renal impairment. In patients with an adjusted creatinine clearance of 50–70 ml/min/1.73 m², administration should commence at a dose of 100 mg twice daily in patients with type 1 Gaucher disease.

In patients with an adjusted creatinine clearance of 30–50 ml/min/1.73 m², administration should commence at a dose of 100 mg once daily in patients with type 1 Gaucher disease. Use in patients with severe renal impairment (creatinine clearance < 30 ml/min/1.73 m²) is not recommended (see sections 4.4 and 5.2).

Hepatic impairment

Miglustat Gen.Orph has not been evaluated in patients with hepatic impairment.

Method of administration

Miglustat Gen.Orph can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Tremor

Approximately 37% of patients in clinical trials in type 1 Gaucher disease reported tremor on treatment. These tremors were described as an exaggerated physiological tremor of the hands. Tremor usually began within the first month, and in many cases resolved during treatment after between 1 and 3 months. Dose reduction may ameliorate the tremor, usually within days, but discontinuation of treatment may sometimes be required.

Gastrointestinal disturbances

Gastrointestinal events, mainly diarrhoea, have been observed in more than 80% of patients, either at the outset of treatment or intermittently during treatment (see section 4.8). The mechanism is most likely inhibition of intestinal disaccharidases such as sucrase-isomaltase in the gastrointestinal tract leading to reduced absorption of dietary disaccharides. In clinical practice, miglustat-induced gastrointestinal events have been observed to respond to individualised diet modification (for example reduction of sucrose, lactose and other carbohydrate intake), to taking miglustat between meals, and/or to anti-diarrhoeal medicinal products such as loperamide. In some patients, temporary dose reduction may be necessary. Patients with chronic diarrhoea or other persistent gastrointestinal events that do not respond to these interventions should be investigated according to clinical practice. Miglustat has not been evaluated in patients with a history of significant gastrointestinal disease, including inflammatory bowel disease.

Effects on spermatogenesis

Male patients should maintain reliable contraceptive methods while taking Miglustat Gen.Orph. Studies in the rat have shown that miglustat adversely affects spermatogenesis and sperm parameters, and reduces fertility (see sections 4.6 and 5.3). Until further information is available, before seeking to conceive, male patients should cease Miglustat Gen.Orph and maintain reliable contraceptive methods for a further 3 months.

Special populations

Due to limited experience, Miglustat Gen.Orph should be used with caution in patients with renal or hepatic impairment. There is a close relationship between renal function and clearance of miglustat, and exposure to miglustat is markedly increased in patients with severe renal impairment (see section 5.2). At present, there is insufficient clinical experience in these patients to provide dosing recommendations. Use of Miglustat Gen.Orph in patients with severe renal impairment (creatinine clearance < 30 ml/min/1.73 m²) is not recommended.

Type 1 Gaucher disease

Although no direct comparisons with Enzyme Replacement Therapy (ERT) have been performed in treatment-naïve patients with type 1 Gaucher disease, there is no evidence of miglustat having an efficacy or safety advantage over ERT. ERT is the standard of care for patients who require treatment

for type 1 Gaucher disease (see section 5.1). The efficacy and safety of miglustat has not been specifically evaluated in patients with severe Gaucher disease.

Regular monitoring of vitamin B₁₂ level is recommended because of the high prevalence of vitamin B₁₂ deficiency in patients with type 1 Gaucher disease.

Cases of peripheral neuropathy have been reported in patients treated with miglustat with or without concurrent conditions such as vitamin B₁₂ deficiency and monoclonal gammopathy. Peripheral neuropathy seems to be more common in patients with type 1 Gaucher disease compared to the general population. All patients should undergo baseline and repeat neurological evaluation.

In patients with type 1 Gaucher disease, monitoring of platelet counts is recommended. Mild reductions in platelet counts without association with bleeding were observed in patients with type 1 Gaucher disease who were switched from ERT to miglustat.

4.5 Interaction with other medicinal products and other forms of interaction

Limited data suggest that co-administration of miglustat and enzyme replacement with imiglucerase in patients with type 1 Gaucher disease may result in decreased exposure to miglustat (approximate reductions of 22% in C_{max} and 14% in AUC were observed in a small parallel-group study). This study also indicated that miglustat has no or limited effect on the pharmacokinetics of imiglucerase.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of miglustat in pregnant women. Studies in animals have shown reproductive toxicity, including dystocia (see section 5.3). The potential risk for humans is unknown. Miglustat crosses the placenta and should not be used during pregnancy.

Breast-feeding

It is not known if miglustat is secreted in breast milk. Miglustat Gen.Orph should not be taken during breast-feeding.

Fertility

Studies in the rat have shown that miglustat adversely affects sperm parameters (motility and morphology) thereby reducing fertility (see sections 4.4 and 5.3). Until further information is available, it is advised that before seeking to conceive, male patients should cease Miglustat Gen.Orph and maintain reliable contraceptive methods for 3 months thereafter.

Contraceptive measures should be used by women of childbearing potential. Male patients should maintain reliable contraceptive methods while taking Miglustat Gen.Orph (see sections 4.4 and 5.3).

4.7 Effects on ability to drive and use machines

Miglustat Gen.Orph has negligible influence on the ability to drive and use machines. Dizziness has been reported as a common adverse reaction, and patients suffering from dizziness should not drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions reported in clinical studies with miglustat were diarrhoea, flatulence, abdominal pain, weight loss and tremor (see section 4.4). The most common serious adverse reaction reported with miglustat treatment in clinical studies was peripheral neuropathy (see section 4.4).

In 11 clinical trials in different indications 247 patients were treated with miglustat at dosages of 50-200 mg t.i.d. for an average duration of 2.1 years. Of these patients, 132 had type 1 Gaucher disease. Adverse reactions were generally of mild to moderate severity and occurred with similar frequency across indications and dosages tested.

Tabulated list of adverse reactions

Adverse reactions from clinical trials and spontaneous reporting, occurring in >1% of patients, are listed in the table below by system organ class and frequency (very common: $\geq 1/10$, common: $\geq 1/100 < 1/10$, uncommon: $\geq 1/1,000$ to $<1/100$, rare: $\geq 1/10,000$ to $<1/1,000$, very rare: $<1/10,000$). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Blood and lymphatic system disorders

Common Thrombocytopenia

Metabolism and nutrition disorders

Very common Weight loss, decreased appetite

Psychiatric disorders

Common Depression, insomnia, libido decreased

Nervous system disorders

Very common Tremor,
Common Peripheral neuropathy, ataxia, amnesia, paraesthesia, hypoaesthesia, headache, dizziness

Gastrointestinal disorders

Very common Diarrhoea, flatulence, abdominal pain
Common Nausea, vomiting, abdominal distension/discomfort, constipation, dyspepsia

Musculoskeletal and connective tissue disorders

Common Muscle spasms, muscle weakness

General disorders and administration site reactions

Common Fatigue, asthenia, chills and malaise

Investigations

Common Nerve conduction studies abnormal

Description of selected adverse reactions

Weight loss has been reported in 55% of patients. The greatest prevalence was observed between 6 and 12 months.

Miglustat has been studied in indications where certain events reported as adverse reactions, such as neurological and neuropsychological symptoms/signs, cognitive dysfunction and thrombocytopenia could also be due to the underlying conditions.

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

No acute symptoms of overdose have been identified. Miglustat has been administered at doses of up to 3000 mg/day for up to six months in HIV positive patients during clinical trials. Adverse events observed included granulocytopenia, dizziness and paraesthesia. Leukopenia and neutropenia have also been observed in a similar group of patients receiving 800 mg/day or higher dose.

Management

In case of overdose general medical care is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Type 1 Gaucher disease is an inherited metabolic disorder caused by a failure to degrade glucosylceramide resulting in lysosomal storage of this material and widespread pathology. Miglustat is an inhibitor of glucosylceramide synthase, the enzyme responsible for the first step in the synthesis of most glycolipids. *In vitro*, glucosylceramide synthase is inhibited by miglustat with an IC_{50} of 20-37 μ M. In addition, inhibitory action on a non-lysosomal glycosylceramidase has been demonstrated experimentally *in vitro*. The inhibitory action on glucosylceramide synthase forms the rationale for substrate reduction therapy in Gaucher disease.

The pivotal trial of miglustat was conducted in patients unable or unwilling to receive ERT. Reasons for not receiving ERT included the burden of intravenous infusions and difficulties in venous access. Twenty-eight patients with mild to moderate type 1 Gaucher disease were enrolled in this 12-month non-comparative study, and 22 patients completed the study. At 12 months, there was a mean reduction in liver organ volume of 12.1% and a mean reduction in spleen volume of 19.0%. A mean increase in haemoglobin concentration of 0.26 g/dl and a mean platelet count increase of $8.29 \times 10^9/l$ were observed. Eighteen patients then continued to receive miglustat under an optional extended treatment protocol. Clinical benefit has been assessed at 24 and 36 months in 13 patients. After 3 years of continuous miglustat treatment, mean reductions in liver and spleen organ volume were 17.5% and 29.6%, respectively. There was a mean increase of $22.2 \times 10^9/l$ in platelet count, and a mean increase of 0.95 g/dl in haemoglobin concentration.

A second open, controlled study randomised 36 patients who had received a minimum of 2 years of treatment with ERT, into three treatment groups: continuation with imiglucerase, imiglucerase in combination with miglustat, or switch to miglustat. This study was conducted over a 6-month randomised comparison period followed by 18 months extension where all patients received miglustat monotherapy. In the first 6 months in patients who were switched to miglustat, liver and spleen organ volumes and haemoglobin levels were unchanged. In some patients there were reductions in platelet count and increases in chitotriosidase activity indicating that miglustat monotherapy may not maintain the same control of disease activity in all patients. 29 patients continued in the extension period. When compared to the measurements at 6 months, disease control was unchanged after 18 and 24 months of miglustat monotherapy (20 and 6 patients, respectively). No patient showed rapid deterioration of type 1 Gaucher disease following the switch to miglustat monotherapy.

A total daily dose of 300 mg miglustat administered in three divided doses was used in the above two studies. An additional monotherapy study was performed in 18 patients at a total daily dose of 150 mg, and results indicate reduced efficacy compared to a total daily dose of 300 mg.

An open-label, non comparative, 2-year study enrolled 42 patients with type 1 Gaucher disease, who had received a minimum of 3 years of ERT and who fulfilled criteria of stable disease for at least 2 years. The patients were switched to monotherapy with miglustat 100 mg t.i.d. Liver volume (primary efficacy variable) was unchanged from baseline to the end of treatment. Six patients had miglustat treatment prematurely discontinued for potential disease worsening, as defined in the study. Thirteen patients discontinued treatment due to an adverse event. Small mean reductions in

haemoglobin [-0.95 g/dL (95% CI: -1.38 , -0.53)] and platelet count [$-44.1 \times 10^9/L$ (95% CI: -57.6 , -30.7)] were observed between baseline and end of study. Twenty-one patients completed 24 months of miglustat treatment. Of these, 18 patients at baseline were within established therapeutic goals for liver and spleen volume, haemoglobin levels, and platelet counts, and 16 patients remained within all these therapeutic goals at Month 24.

Bone manifestations of type 1 Gaucher disease were evaluated in 3 open-label clinical studies in patients treated with miglustat 100 mg t.i.d. for up to 2 years ($n = 72$). In a pooled analysis of uncontrolled data, bone mineral density Z-scores at the lumbar spine and femoral neck increased by more than 0.1 units from baseline in 27 (57%) and 28 (65%) of the patients with longitudinal bone density measurements. There were no events of bone crisis, avascular necrosis or fracture during the treatment period.

5.2 Pharmacokinetic properties

Pharmacokinetic parameters of miglustat were assessed in healthy subjects, in a small number of patients with type 1 Gaucher disease, Fabry disease, HIV-infected patients, and in adults, adolescents and children with type 3 Gaucher disease.

The kinetics of miglustat appear to be dose linear and time independent. In healthy subjects miglustat is rapidly absorbed. Maximum plasma concentrations are reached about 2 hours after dose. Absolute bioavailability has not been determined. Concomitant administration of food decreases the rate of absorption (C_{max} was decreased by 36% and t_{max} delayed 2 hours), but has no statistically significant effect on the extent of absorption of miglustat (AUC decreased by 14%).

The apparent volume of distribution of miglustat is 83 l. Miglustat does not bind to plasma proteins. Miglustat is mainly eliminated by renal excretion, with urinary recovery of unchanged drug accounting for 70-80% of the dose. Apparent oral clearance (CL/F) is 230 ± 39 ml/min. The average half-life is 6–7 hours.

Following administration of a single dose of 100 mg ^{14}C -miglustat to healthy volunteers, 83% of the radioactivity was recovered in urine and 12% in faeces. Several metabolites were identified in urine and faeces. The most abundant metabolite in urine was miglustat glucuronide accounting for 5% of the dose. The terminal half-life of radioactivity in plasma was 150 h suggesting the presence of one or more metabolites with very long half-life. The metabolite accounting for this has not been identified, but may accumulate and reach concentrations exceeding those of miglustat at steady state.

The pharmacokinetics of miglustat is similar in adult type 1 Gaucher disease patients when compared to healthy subjects.

Paediatric population

Pharmacokinetic data were obtained in paediatric patients with type 3 Gaucher disease aged 3 to 15 years. At steady state, the concentration of miglustat in cerebrospinal fluid of six type 3 Gaucher disease patients was 31.4–67.2% of that in plasma.

Limited data in patients with Fabry disease and impaired renal function showed that CL/F decreases with decreasing renal function. While the numbers of subjects with mild and moderate renal impairment were very small, the data suggest an approximate decrease in CL/F of 40% and 60% respectively, in mild and moderate renal impairment (see section 4.2). Data in severe renal impairment are limited to two patients with creatinine clearance in the range 18 – 29 ml/min and cannot be extrapolated below this range. These data suggest a decrease in CL/F by at least 70% in patients with severe renal impairment.

Over the range of data available, no significant relationships or trends were noted between miglustat pharmacokinetic parameters and demographic variables (age, BMI, gender or race).

There are no pharmacokinetic data available in patients with liver impairment, in children or adolescents with type 1 Gaucher disease or in the elderly (> 70 years).

5.3 Preclinical safety data

The main effects common to all species were weight loss and diarrhoea, and, at higher doses, damage to the gastrointestinal mucosa (erosions and ulceration). Further effects seen in animals at doses that result in exposure levels similar to or moderately higher than the clinical exposure level were: changes in lymphoid organs in all species tested, transaminase changes, vacuolation of thyroid and pancreas, cataracts, nephropathy and myocardial changes in rats. These findings were considered to be secondary to debilitation.

Administration of miglustat to male and female Sprague-Dawley rats by oral gavage for 2 years at dose levels of 30, 60 and 180 mg/kg/day resulted in an increased incidence of testicular interstitial cell (Leydig cell) hyperplasia and adenomas in male rats at all dose levels. The systemic exposure at the lowest dose was below or comparable to that observed in humans (based on AUC_{0-∞}) at the recommended human dose. A No Observed Effect Level (NOEL) was not established and the effect was not dose dependent. There was no drug-related increase in tumor incidence in male or female rats in any other organ. Mechanistic studies revealed a rat specific mechanism which is considered to be of low relevance for humans.

Administration of miglustat to male and female CD1 mice by oral gavage at dose levels of 210, 420 and 840/500 mg/kg/day (dose reduction after half a year) for 2 years resulted in an increased incidence of inflammatory and hyperplastic lesions in the large intestine in both sexes. Based on mg/kg/day and corrected for differences in faecal excretion, the doses corresponded to 8, 16 and 33/19 times the highest recommended human dose (200 mg t.i.d.). Carcinomas in the large intestine occurred occasionally at all doses with a statistically significant increase in the high dose group. A relevance of these findings to humans cannot be excluded. There was no drug-related increase in tumour incidence in any other organ.

Miglustat did not show any potential for mutagenic or clastogenic effects in the standard battery of genotoxicity tests.

Repeated-dose toxicity studies in rats showed effects on the seminiferous epithelium of the testes. Other studies revealed changes in sperm parameters (motility and morphology) consistent with an observed reduction in fertility. These effects occurred at exposure levels similar to those in patients, but showed reversibility. Miglustat affected embryo/foetal survival in rats and rabbits, dystocia was reported, post-implantation losses were increased, and an increased incidence of vascular anomalies occurred in rabbits. These effects may be partly related to maternal toxicity.

Changes in lactation were observed in female rats in a 1-year study. The mechanism for this effect is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Sodium starch glycolate (Type A),
Povidone (K30),
Magnesium stearate.

Capsule shell

Gelatin,
Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polyamide/aluminium/PVC/Aluminium blister supplied as a box of 12 blisters, each blister containing 7 capsules providing a total of 84 capsules.

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

Gen.Orph
185 Bureaux de la Colline
92213 Saint Cloud Cedex
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1232/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: { 10 november 2017 }

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

Delpharm Reims
10 rue Colonel Charbonneaux
51100 Reims
France

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**

The requirements for submission of periodic safety update reports 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.

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

- **Risk Management Plan (RMP)**

The 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

Miglustat Gen.Orph 100 mg hard capsules

miglustat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 100 mg miglustat

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule.
84 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

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

Gen.Orph
185 Bureaux de la Colline
92213 Saint Cloud Cedex
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1232/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Miglustat Gen.Orph

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Miglustat Gen.Orph 100 mg hard capsules

miglustat

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Gen.Orph

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Miglustat Gen.Orph 100 mg hard capsules miglustat

Read all of this leaflet carefully before you start taking 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 or pharmacist.
- 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 or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Miglustat Gen.Orph is and what it is used for
2. What you need to know before you take Miglustat Gen.Orph
3. How to take Miglustat Gen.Orph
4. Possible side effects
5. How to store Miglustat Gen.Orph
6. Contents of the pack and other information

1. What Miglustat Gen.Orph is and what it is used for

Miglustat Gen.Orph contains the active substance miglustat which belongs to a group of medicines that affect metabolism. It is used to treat mild to moderate type 1 Gaucher disease in adults.

In type 1 Gaucher disease, a substance called glucosylceramide is not removed from your body. It starts to build up in certain cells of the body's immune system. This can result in liver and spleen enlargement, changes in the blood and bone disease.

The usual treatment for type 1 Gaucher disease is enzyme replacement therapy. Miglustat Gen.Orph is only used when a patient is considered unsuitable for treatment with enzyme replacement therapy.

2. What you need to know before you take Miglustat Gen.Orph

Do not take Miglustat Gen.Orph

- if you are allergic to miglustat or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your doctor or pharmacist before taking Miglustat Gen.Orph

- if you suffer from kidney disease
- if you suffer from liver disease

Your doctor will perform the following tests before treatment and during treatment with Miglustat Gen.Orph:

- an examination to check the nerves in your arms and legs
- measurement of vitamin B₁₂ levels
- monitoring of blood platelet counts

The reason for these tests is that some patients have had tingling or numbness in the hands and feet, or a decrease in body weight, while taking Miglustat Gen.Orph. The tests will help the doctor decide

whether these effects are due to your disease or other existing conditions, or due to side effects of Miglustat Gen.Orph (see section 4 for further details).

If you have diarrhoea, your doctor may ask you to change your diet to reduce your lactose and carbohydrate intake such as sucrose (cane sugar), or not to take Miglustat Gen.Orph together with food, or to temporarily reduce your dose. In some cases the doctor may prescribe anti-diarrhoeal medicines such as loperamide. If your diarrhoea does not respond to these measures, or if you have any other abdominal complaint, consult your doctor. In such case, your doctor may decide to conduct further investigations.

Male patients should use reliable birth control methods during their treatment with Miglustat Gen.Orph, and for 3 months after finishing treatment.

Children and adolescents

Do not give this medicine to children and adolescents (below 18 years old) with type 1 Gaucher disease because it is not known if it works in this disease.

Other medicines and Miglustat Gen.Orph

Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines.

Tell your doctor if you are taking medicines containing imiglucerase, which are sometimes used at the same time as Miglustat Gen.Orph. They may lower the amount of Miglustat Gen.Orph in your body.

Pregnancy, breast-feeding and fertility

You should not take Miglustat Gen.Orph if you are pregnant or thinking of becoming pregnant. Your doctor can give you more information. You must use effective birth control while taking Miglustat Gen.Orph. Do not breastfeed while you are taking Miglustat Gen.Orph.

Male patients should use reliable birth control methods during their treatment with Miglustat Gen.Orph, and for 3 months after finishing treatment.

If you are pregnant, breast feeding, think you may be pregnant or planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

Miglustat Gen.Orph may make you feel dizzy. Do not drive or use any tools or machines if you feel dizzy.

3. How to take Miglustat Gen.Orph

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

In type 1 Gaucher disease: for adults, the usual dose is one capsule (100 mg) three times a day (morning, afternoon and evening). This means a daily maximum of three capsules (300 mg).

If you have a problem with your kidneys you may receive a lower starting dose. Your doctor may reduce your dose, e.g., to one capsule (100 mg) once or twice a day, if you suffer from diarrhoea when taking Miglustat Gen.Orph (see section 4). Your doctor will tell you how long your treatment will last.

Miglustat Gen.Orph can be taken with or without food. You should swallow the whole capsule with a glass of water.

If you take more Miglustat Gen.Orph than you should

If you take more capsules than you were told to, consult your doctor immediately. Miglustat has been used in clinical trials at doses ten times higher than the recommended dose: this caused decreases in white blood cells and other side effects similar to those described in section 4.

If you forget to take Miglustat Gen.Orph

Take the next capsule at the usual time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Miglustat Gen.Orph

Don't stop taking Miglustat Gen.Orph without talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

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

Most serious side effects:

Some patients have had tingling or numbness in the hands and feet (seen commonly). They could be signs of peripheral neuropathy, due to side effects of Miglustat Gen.Orph or they could be due to existing conditions. Your doctor will perform some tests before and during treatment with Miglustat Gen.Orph to assess this (see section 2).

If you do get any of these effects, please seek medical advice from your doctor as soon as possible.

If you get a slight tremor, usually trembling hands, seek medical advice from your doctor as soon as possible. The tremor often disappears without needing to stop the treatment. Sometimes your doctor will need to reduce the dose or stop Miglustat Gen.Orph treatment to stop the tremor.

Very common effects may affect more than 1 in 10 people.

The most common side effects are diarrhoea, flatulence (wind), abdominal (stomach) pain, weight loss and decreased appetite.

If you do lose some weight when you start treatment with Miglustat Gen.Orph don't worry. People usually stop losing weight as treatment goes on.

Common effects may affect up to 1 in 10 people.

Common side effects of treatment include headache, dizziness, paraesthesia (tingling or numbness), abnormal coordination, hypoaesthesia (reduced sensation to touch), dyspepsia (heartburn), nausea (feeling sick), constipation and vomiting, swelling or discomfort in the abdomen (stomach) and thrombocytopenia (reduced levels of blood platelets). The neurological symptoms and thrombocytopenia could be due to the underlying disease.

Other possible side effects are muscular spasms or weakness, fatigue, chills and malaise, depression, difficulty sleeping, forgetfulness and less libido.

Most patients get one or more of these side effects, usually at the start of treatment or at intervals during treatment. Most cases are mild and disappear quite quickly. If any of these side effects cause problems, consult your doctor. He or she may reduce the dose of Miglustat Gen.Orph or recommend other medicines to help control side effects.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. 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 Miglustat Gen.Orph

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

Do not take this medicine after the expiry date which is stated on the carton after 'EXP'. The expiry date refers to the last day 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 you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Miglustat Gen.Orph contains

- The active substance is miglustat 100 mg.
- The other ingredients are sodium starch glycolate (type A), povidone (K30), magnesium stearate, gelatin, titanium dioxide (E171).

What Miglustat Gen.Orph looks like and contents of the pack

Miglustat Gen.Orph 100 mg hard capsules are white opaque cap and body, hard gelatin capsules size 4 of 14.0 mm length.

Box of 12 blisters, each blister containing 7 capsules providing a total of 84 capsules.

Marketing Authorisation Holder

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185 Bureaux de la Colline
92213 Saint Cloud Cedex
France

Manufacturer

Delpharm Reims
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For any information about this medicine, please contact the Marketing Authorisation Holder.

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This leaflet was last revised in {month YYYY}.

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.