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 hard 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 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).

Miglustat Gen.Orph is indicated for the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease (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 or Niemann-Pick type C disease, as appropriate.

Posology

Dose in type 1 Gaucher disease

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.

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

Dose in Niemann-Pick type C disease

Adult
The recommended dose for the treatment of adult patients with Niemann-Pick type C disease is 200 mg three times a day.

Paediatric population
The recommended dose for the treatment of adolescent patients (12 years of age and above) with Niemann-Pick type C disease is 200 mg three times a day.

Dosing in patients under the age of 12 years should be adjusted on the basis of body surface area as illustrated below:

Table 1. – Paediatric population

Body surface area (m^2)	Recommended dose
> 1.25	200 mg three times a day
> 0.88 – 1.25	200 mg twice a day
> 0.73 – 0.88	100 mg three times a day
> 0.47 – 0.73	100 mg twice a day
≤ 0.47	100 mg once a day

Temporary dose reduction may be necessary in some patients because of diarrhoea.

The benefit to the patient of treatment with miglustat should be evaluated on a regular basis (see section 4.4).

There is limited experience with the use of miglustat in Niemann-Pick type C disease patients under the age of 4 years.

Special populations

Elderly
There is no experience with the use of miglustat 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 m^2, administration should commence at a dose of 100 mg twice daily in patients with type 1 Gaucher disease and at a dose of 200 mg twice daily (adjusted for body surface area in patients below the age of 12) in patients with Niemann-Pick type C disease.

In patients with an adjusted creatinine clearance of 30–50 mL/min/1.73 m^2, administration should commence at a dose of 100 mg once daily in patients with type 1 Gaucher disease and at a dose of 100 mg twice daily (adjusted for body surface area in patients below the age of 12) in patients with Niemann-Pick type C disease. Use in patients with severe renal impairment (creatinine clearance < 30 mL/min/1.73 m^2) is not recommended (see sections 4.4 and 5.2).

Hepatic impairment
Miglustat has not been evaluated in patients with hepatic impairment.

Method of administration

Oral use.
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 studies in type 1 Gaucher disease, and 58% of patients in a clinical study in Niemann-Pick type C disease reported tremor on treatment. In type 1 Gaucher disease, these tremors were described as an exaggerated physiological tremor of the hands. Tremor usually began within the first month of treatment, and in many cases resolved after 1 to 3 months of continued treatment. 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.

Cases of Crohn's disease have been reported post-marketing in Niemann-Pick type C disease patients treated with Miglustat Gen.Orph. Gastrointestinal disturbances are common adverse events of Miglustat Gen.Orph. Therefore, in patients with chronic diarrhoea and/or abdominal pain that do not respond to interventions or in the event of clinical worsening, the possibility of Crohn's disease should be considered.

Effects on spermatogenesis

Reliable contraceptive methods should be maintained while male patients are taking miglustat and for 3 months following discontinuation. Miglustat should be discontinued and reliable contraception be used for the next 3 months before attempting to conceive (see sections 4.6 and 5.3). Studies in the rat have shown that miglustat adversely affects spermatogenesis and sperm parameters, and reduces fertility (see sections 4.6 and 5.3).

Special populations

Due to limited experience, miglustat 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 in patients with severe renal impairment (creatinine clearance < 30 mL/min/1.73 m^2) is not recommended.

Type 1 Gaucher disease

Although no direct comparisons with Enzyme Replacement Therapy (ERT) have been performed in treatment-naive 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 B_{12} level is recommended because of the high prevalence of vitamin B_{12} 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 B_{12} 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.

Niemann-Pick type C disease

The benefit of treatment with miglustat for neurological manifestations in patients with Niemann-Pick type C disease should be evaluated on a regular basis, e.g. every 6 months; continuation of therapy should be re-appraised after at least 1 year of treatment with miglustat.

Mild reductions in platelet counts without association to bleeding were observed in some patients with Niemann-Pick type C disease treated with miglustat. In patients included in the clinical study, 40%-50% had platelet counts below the lower limit of normal at baseline. Monitoring of platelet counts is recommended in these patients.

Reduced growth in the paediatric population

Reduced growth has been reported in some paediatric patients with Niemann-Pick type C disease in the early phase of treatment with miglustat where the initial reduced weight gain may be accompanied or followed by reduced height gain. Growth should be monitored in paediatric and adolescent patients during treatment with miglustat; the benefit/risk balance should be re-assessed on an individual basis for continuation of therapy.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per hard capsule, that is to say essentially 'sodium-free'.

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 Cmax 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 maternal and embryo-foetal toxicity, including decreased embryo-foetal survival (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).

Contraception in males and females

Contraceptive measures should be used by women of childbearing potential. Reliable contraceptive methods should be maintained while male patients are taking Miglustat Gen.Orph and for 3 months following discontinuation (see sections 4.4 and 5.3).

4.7 Effects on ability to drive and use machines

Miglustat 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 studies in different indications 247 patients were treated with miglustat at doses of 50-200 mg three times a day (t.i.d.) for an average duration of 2.1 years. Of these patients, 132 had type 1 Gaucher disease, and 40 had Niemann-Pick type C disease. Adverse reactions were generally of mild to moderate severity and occurred with similar frequency across indications and doses tested.

Tabulated list of adverse reactions

Adverse reactions from clinical studies and spontaneous reporting, occurring in > 1% of patients, are listed in the table below by system organ class and frequency (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).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2. - Tabulated list of adverse reactions

System Organ Class (SOC)	Frequency	Adverse reaction
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 disorder	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 studies. 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, various alimentary tract and metabolism products, ATC Code: A16AX06

Clinical efficacy and safety

Type 1 Gaucher disease

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 μM. 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 study 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 8.29×10^9/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 × 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 × $10^{9/}$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.

Niemann-Pick type C disease

Niemann-Pick type C disease is a very rare, invariably progressive and eventually fatal neurodegenerative disorder characterised by impaired intracellular lipid trafficking. The neurological manifestations are considered secondary to the abnormal accumulation of glycosphingolipids in neuronal and glial cells.

Data to support safety and efficacy of miglustat in Niemann-Pick type C disease come from a prospective open-label clinical study and a retrospective survey. The clinical study included 29 adult and juvenile patients in a 12-month controlled period, followed by extension therapy for an average total duration of 3.9 years and up to 5.6 years. In addition 12 paediatric patients were enrolled in an uncontrolled substudy for an overall average duration of 3.1 years and up to 4.4 years. Among the 41 patients enrolled in the study 14 patients were treated with miglustat for more than 3 years. The survey included a case series of 66 patients treated with miglustat outside of the clinical study for a mean duration of 1.5 years. Both data sets included paediatric, adolescent and adult patients with an

age range of 1 year to 43 years. The usual dose of miglustat in adult patients was 200 mg t.i.d., and was adjusted according to body surface area in paediatric patients.

Overall the data show that treatment with miglustat can reduce the progression of clinically relevant neurological symptoms in patients with Niemann-Pick type C disease.

The benefit of treatment with miglustat for neurological manifestations in patients with Niemann-Pick type C disease should be evaluated on a regular basis, e.g. every 6 months; continuation of therapy should be re-appraised after at least 1 year of treatment with miglustat, (see section 4.4).

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 Niemann-Pick type C disease or 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 active substance 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 and Niemann-Pick type C disease patients when compared to healthy subjects.

<u>Paediatric population</u>

Pharmacokinetic data were obtained in paediatric patients with type 3 Gaucher disease aged 3 to 15 years, and patients with Niemann-Pick type C disease aged 5–16 years. Dosing in children at 200 mg t.i.d. adjusted for body surface area resulted in C_{max} and AUC_{τ} values which were approximately twofold those attained after 100 mg t.i.d. in type 1 Gaucher disease patients, consistent with the dose-linear pharmacokinetics of miglustat. 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 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 AUC0-∞) 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 seminiferous tubule degeneration and atrophy. Other studies revealed changes in sperm parameters (sperm concentration, motility and morphology) consistent with an observed reduction in fertility. These effects occurred at dose levels adjusted for body surface area similar to those in patients, but showed reversibility. Miglustat decreased embryo/foetal survival in rats and rabbits. Prolonged parturition 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

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

Polyamide/aluminium/PVC/Aluminium blister containing 7 (perforated unit dose) or 7 (non-perforated) capsules.

Pack size of 84 hard capsules in non-perforated blisters.
Pack size of 84x1 hard capsules in perforated unit dose blisters

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

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1232/001
EU/1/17/1232/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 november 2017
Date of latest renewal: 19 September 2022

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. MANUFACTURERS 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. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Delpharm Reims
10 rue Colonel Charbonneaux
51100 Reims
France

Centre Lab
ZA Granderaie
23000 Guéret
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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.

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

Miglustat Gen.Orph 100 mg hard capsules

miglustat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 100 mg miglustat

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule.
84 hard capsules
84x1 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

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
EU/1/17/1232/002

13. BATCH NUMBER

Lot

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
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (non-perforated blisters)
BLISTERS (perforated unit dose blisters)

1. NAME OF THE MEDICINAL PRODUCT

Miglustat Gen.Orph 100 mg hard capsules

miglustat

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Gen.Orph (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

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

Miglustat Gen.Orph contains the active substance miglustat which belongs to a group of medicines that affect metabolism. It is used to treat two conditions:

- **Miglustat Gen.Orph 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.

- **Miglustat Gen.Orph is also used to treat progressive neurological symptoms in Niemann-Pick type C disease in adults and in children.**

If you have Niemann-Pick type C disease, fats such as glycosphingolipids build up in the cells of your brain. This can result in disturbances in neurological functions such as slow eye movements, balance, swallowing, and memory, and in seizures.

Miglustat Gen.Orph works by inhibiting the enzyme called 'glucosylceramide synthase' which is responsible for the first step in the synthesis of most glycosphingolipids.

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 growth if you are a child or adolescent with Niemann-Pick type C disease
- 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. Cases of Crohn's disease (an inflammatory disease affecting the gut) have been reported in patients with Niemann-Pick type C disease treated with Miglustat Gen.Orph. 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 to determine if there is another cause of your symptoms.

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.

Miglustat Gen.Orph contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per hard capsule, that is to say essentially 'sodium-free'.

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.

- **For 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).

- **For Niemann-Pick type C disease**: For adults and adolescents (over 12 years old), the usual dose is two capsules (200 mg) three times a day (morning, afternoon and evening). This means a daily maximum of six capsules (600 mg).

For children **less than 12 years old**, your doctor will adjust the dose for Niemann-Pick type C disease.

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 studies at doses up to 3000 mg: 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). See section 2 "Miglustat Gen.Orph contains sodium".

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 mm length.
Pack size of 84 hard capsules in non-perforated blisters and 84x1 hard capsules in perforated unit dose blisters.

Not all pack sizes may be marketed.

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For any information about this medicine, please contact the local representative of 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.