

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zavesca 100 mg hard capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100 mg miglustat.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

White capsules with “OGT 918” printed in black on the cap and “100” printed in black on the body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Zavesca 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.

Zavesca can be taken with or without food.

Dosage in type 1 Gaucher disease

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.

There is no experience with the use of Zavesca in patients with type 1 Gaucher disease under the age of 18. The use of Zavesca is therefore not recommended in children or adolescents with type 1 Gaucher disease. There is no experience with the use of Zavesca in patients over the age of 70.

Dosage in Niemann-Pick type C disease

The recommended dose for the treatment of adult and adolescent patients 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:

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 Zavesca should be evaluated on a regular basis (see section 4.4).

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

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 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 m², 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 m²) is not recommended (see sections 4.4 and 5.2).

Hepatic Impairment

Zavesca has not been evaluated in patients with hepatic impairment.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

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 Zavesca 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 Zavesca has not been specifically evaluated in patients with severe Gaucher disease.

Approximately 38% of patients in clinical trials in type 1 Gaucher disease, and 58% of patients in a clinical trial 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, 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.

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 Zavesca 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. Patients who develop symptoms such as numbness and tingling should have a careful re-assessment of risk-benefit.

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 probably inhibition of disaccharidases in the gastrointestinal tract. The majority of cases are mild and are expected to resolve spontaneously on therapy. In clinical practice, diarrhoea has been observed to respond to diet modification (reduction of lactose and other carbohydrate intake), to taking Zavesca away from 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. Zavesca has not been evaluated in patients with a history of significant gastrointestinal disease, including inflammatory bowel disease.

Male patients should maintain reliable contraceptive methods while taking Zavesca. 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 Zavesca and maintain reliable contraceptive methods for a further 3 months.

Due to limited experience, Zavesca 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 of 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 Zavesca in patients with severe renal impairment (creatinine clearance < 30 ml/min/1.73 m²) is not recommended.

Niemann-Pick type C disease

The benefit of treatment with Zavesca 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 Zavesca.

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 Zavesca; the benefit/risk balance should be re-assessed on an individual basis for continuation of therapy.

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

4.5 Interaction with other medicinal products and other forms of interaction

Limited data suggest that co-administration of Zavesca and Cerezyme 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 Zavesca has no or limited effect on the pharmacokinetics of Cerezyme.

4.6 Pregnancy and lactation

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. Contraceptive measures should be used by women of childbearing potential.

It is not known if miglustat is secreted in breast milk. Zavesca should not be used during breast-feeding.

Male patients should maintain reliable contraceptive methods while taking Zavesca and for 3 months after finishing treatment (see sections 4.4 and 5.3)

4.7 Effects on ability to drive and use machines

No studies on the effects of Zavesca on the ability to drive or use machines have been performed. However, dizziness has been reported as a very common adverse event, and patients suffering from dizziness should not drive or operate machinery.

4.8 Undesirable effects

In nine clinical trials in different indications 206 patients were treated with Zavesca at dosages of 50-200 mg t.i.d. for an average duration of 2.2 years. Of these patients, 90 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 dosages tested. The most common adverse reactions were gastrointestinal, with diarrhoea and other abdominal complaints, and weight loss.

Adverse drug reactions, defined as treatment-emergent adverse events reported as related to treatment by the investigator and occurring in >1% of patients, are listed in the table below by body system and frequency (very common: $\geq 1/10$, common: $\geq 1/100 < 1/10$). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

<u>Blood and lymphatic system disorders</u>	
Common	Thrombocytopenia
<u>Metabolism and Nutrition Disorders</u>	
Very common	Weight loss
Common	Anorexia, decreased appetite
<u>Psychiatric disorders</u>	
Common	Insomnia, libido decreased
<u>Nervous System Disorders</u>	
Very common	Tremor,
Common	Peripheral neuropathy, headache, paraesthesia, dizziness, ataxia, hypoaesthesia
<u>Gastrointestinal Disorders</u>	
Very common	Diarrhoea, flatulence, abdominal pain
Common	Nausea, vomiting, abdominal distension/discomfort, constipation, dyspepsia
<u>Musculoskeletal and connective tissue disorders</u>	
Common	Muscle spasms
<u>General disorders and administration site reactions</u>	

Common:	Fatigue, asthenia
<u>Investigations</u>	
Common	Nerve conduction studies abnormal,

Weight loss has been observed in approximately 60% of patients. The greatest effect was at 12 months, with a mean weight loss of 6–7% of body weight, with a subsequent tendency for an increase in weight towards the baseline value.

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

Isolated cases of cognitive dysfunction have been reported during clinical trials of Zavesca in type 1 Gaucher disease. A causal relationship to Zavesca has not been established.

4.9 Overdose

No acute symptoms of overdose have been identified. Zavesca 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

This medicinal product has been authorised under “Exceptional Circumstances”. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency (EMA) will review any new information, which may become available every year and this SPC will be updated as necessary.

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 IC₅₀ 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 trial of Zavesca 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 × 10⁹/l were observed. Eighteen patients then continued to receive Zavesca under an optional extended treatment protocol. Clinical benefit has been assessed at 24 and 36 months in 13 patients. After 3 years of continuous Zavesca treatment, mean reductions in liver and spleen organ volume were 17.5% and 29.6%, respectively. There was a mean increase of 22.2 × 10⁹/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 Cerezyme, Cerezyme in combination with Zavesca, or switch to Zavesca. This study was conducted over a 6-month randomised comparison period followed by 18 months extension where all patients received Zavesca monotherapy. In the first 6 months in patients who were switched to Zavesca, 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 Zavesca 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 Zavesca monotherapy (20 and 6 patients, respectively). No patient showed rapid deterioration of type 1 Gaucher disease following the switch to Zavesca monotherapy.

A total daily dose of 300 mg Zavesca 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.

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 Zavesca in Niemann-Pick type C disease come from a prospective open-label clinical trial and a retrospective survey. The clinical trial 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 trial 14 patients were treated with Zavesca for more than 3 years. The survey included a case series of 66 patients treated with Zavesca outside of the clinical trial 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 Zavesca 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 Zavesca can reduce the progression of clinically relevant neurological symptoms in patients with Niemann-Pick type C disease.

The benefit of treatment with Zavesca 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 Zavesca, (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 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 and Niemann-Pick type C disease patients when compared to healthy subjects. 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 two-fold 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 $\text{AUC}_{0-\infty}$) 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 tumour 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 glycollate,
Povidone (K30),
Magnesium stearate.

Capsule shell:

Gelatin,
Water,
Titanium dioxide (E171).

Printing ink:

Black iron oxide (E172)
Shellac.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30 °C.

6.5 Nature and contents of container

ACLAR/ALU blister strips supplied as a box of 4 blister strips, each blister strip containing 21 capsules providing a total of 84 capsules.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Actelion Registration Ltd
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United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/238/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 November 2002

20 November 2007

10. DATE OF REVISION OF THE TEXT

May 2009