# AUSTRALIAN PRODUCT INFORMATION

# ZAVESCA®

# Miglustat

# 100 mg capsules

## 1 NAME OF THE MEDICINE

Miglustat

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active: 100 mg miglustat

For the full list of excipients, see **6.1 LIST OF EXCIPIENTS**.

## 3 PHARMACEUTICAL FORM

Hard capsules.

White capsule with "OGT918" printed in black on the cap and "100" printed on the body.

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

ZAVESCA® is indicated for the oral treatment of patients with mild to moderate Type 1 Gaucher disease, for whom enzyme replacement therapy is not a therapeutic option.

ZAVESCA® is indicated for the treatment of progressive neurological manifestations in adult and paediatric patients with Niemann-Pick type C disease.

### 4.2 DOSE AND METHOD OF ADMINSTRATION

Therapy should be directed by physicians who are experienced in the management of Gaucher disease or Niemann-Pick type C disease.

**Dosage in Type 1 Gaucher disease**

***Adults***

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

As there has been no formal food interaction study performed, it is recommended to take ZAVESCA® without food.

Patients should be instructed to reduce the intake of foods which are high in disaccharides (e.g. lactose or sucrose) or to take ZAVESCA® away from food, as these actions have been shown during the clinical studies to reduce the risk and/or intensity of gastrointestinal adverse events.

Also, the use of medications such as loperamide have been demonstrated to be effective in patients experiencing diarrhoea on ZAVESCA®. Temporary dose reduction of ZAVESCA® to 100 mg once or twice a day may be necessary in some patients because of diarrhoea.

***Children, adolescents and the elderly***

There is currently no relevant experience with the use of ZAVESCA® in patients under the age of 18 and over the age of 70. The use of ZAVESCA® is therefore not recommended in children or adolescents with Type 1 Gaucher disease.

**Dosage in Niemann-Pick type C disease**

***Adults and adolescents***

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

***Children***

Dosing in patients under the age of 12 years should be adjusted on the basis of body surface area (BSA, mg/m$^2$) as illustrated below:

| BSA (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 | 300 mg daily divided in 2–3 doses |
| > 0.47 - 0.73 | 100 mg twice a day |
| ≤ 0.47 | 100 mg once a day |

* Body surface area (m$^2$) = 0.007184 x (patient height in cm)$^{0.725}$ x (patient weight in kg)$^{0.425}$

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 (e.g. every 6 months).

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

**Renal impairment (Type 1 Gaucher disease and Niemann-Pick type C disease)**

Pharmacokinetic data indicate increased systemic exposure to miglustat in patients with renal impairment, consistent with the kidneys being the main route of elimination. In patients with an adjusted creatinine clearance of 50-70 mL/min/1.73m$^2$, administration of ZAVESCA® should commence at a dose of 100 mg twice daily. In patients with an adjusted creatinine clearance of 30-50 mL/min/1.73 m$^2$, administration should commence at a dose of one 100 mg capsule per day. If necessary the reduced dose can be achieved by dosing twice or once daily respectively.

Use of ZAVESCA® in patients with severe renal impairment (creatinine clearance < 30 mL/min/1.73 m$^2$) is not recommended owing to a lack of clinical experience.

**Hepatic impairment (Type 1 Gaucher disease and Niemann-Pick type C disease)**

ZAVESCA® has not been evaluated in patients with hepatic impairment, although it is assumed that hepatic impairment will not affect the pharmacokinetics of miglustat, as most of the drug is eliminated unchanged, primarily via the kidneys.

## 4.3 CONTRAINDICATIONS

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

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

**Identified Precautions**

***General***

The efficacy and safety of ZAVESCA® has not been evaluated in patients with severe Type 1 Gaucher disease, defined as haemoglobin concentration <90g/L, platelet count <50 X $10^9$/L and active bone disease. Enzyme replacement therapy remains the standard of care for previously untreated patients with Type 1 Gaucher disease.

***Tremor***

Approximately 38% of patients in clinical trials in Type 1 Gaucher disease, and 58% of patients in a clinical trial of 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. As tremor has also been described in ZAVESCA®-naïve patients with Type 1 Gaucher disease, the presence of pre-existing tremor should be formally investigated prior to the initiation of ZAVESCA® therapy.

***Peripheral Neuropathy***

Peripheral neuropathy seems to be more common in patients with Type 1 Gaucher disease compared to the general population. Cases of peripheral neuropathy have been confirmed by *ad hoc* electrodiagnostic (EDX) testing in patients treated with ZAVESCA®, primarily in those with relevant concurrent conditions, such as vitamin $B_{12}$ deficiency and monoclonal gammopathy. None of these patients had a formal baseline neurological assessment prior to initiation of therapy to exclude pre-existing disease and further, relevant symptoms, including paraesthesia, and EDX-confirmed peripheral neuropathy have been reported in ZAVESCA®-naïve patients with Type 1 Gaucher disease. Nevertheless, all patients receiving ZAVESCA® should undergo formal baseline and repeat neurological evaluation at 6-month intervals. Patients who develop symptoms, or who have an exacerbation of pre-existing symptoms, such as numbness and tingling, on treatment should have a careful re-assessment of risk-benefit.

Monitoring of vitamin $B_{12}$ levels is recommended because of the high prevalence of vitamin $B_{12}$ deficiency in patients with Type 1 Gaucher disease.

***Gastrointestinal Events***

Gastrointestinal events, mainly diarrhoea, have been observed in more than 80% of patients, either at the onset of treatment or intermittently during treatment (see **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**). The mechanism is probably inhibition of disaccharidases in the gastrointestinal tract. 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 ZAVESCA® between meals, and/or to anti-diarrhoeal medication 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.

Cases of Crohn's disease have been reported post-marketing in Niemann-Pick type C disease patients treated with ZAVESCA®. Gastrointestinal disturbances are common adverse events of ZAVESCA®. 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.

***Potential Adverse Effects on Spermatogenesis, Sperm Parameters and Fertility***

Reliable contraceptive methods should be maintained while male patients are taking ZAVESCA® and for 3 months following discontinuation. Studies in the rat have shown that miglustat adversely affects spermatogenesis, sperm parameters (in particular, increases in the number of abnormal sperm) and reduces fertility.

***Type 1 Gaucher disease***

*Haematological events*

Monitoring of platelet counts is recommended in these patients. Mild reductions in platelet counts without association with bleeding were observed in patients with type 1 Gaucher disease who were switched from enzyme replacement therapy (ERT) to Zavesca®.

***Niemann-Pick type C disease***

*Neurological events*

The benefit of treatment with ZAVESCA® for neurological manifestations in patients with NP-C 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®.

*Growth disturbance in paediatric and adolescent patients*

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.

Delayed sexual development was observed in juvenile rats treated with miglustat from prior to weaning to maturity at doses less than the maximal recommended paediatric dose, based on body surface area. The clinical relevance of this finding is unknown.

*Haematological events*

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

**Use in renal impairment**

Miglustat is excreted primarily by the kidneys and thus, renal impairment may affect its clearance. Dose adjustment is therefore recommended in these patients (*see* **4.2 DOSE AND METHOD OF ADMINISTRATION – Renal impairment and 5.2 PHARMACOKINETIC PROPERTIES – Renal impairment**). At present, there is insufficient clinical experience with the administration of ZAVESCA® in patients with severe renal impairment (creatinine clearance < 30 mL/min/1.73 $m^2$) and thus, ZAVESCA® is not recommended in these patients.

**Use in hepatic impairment**

*See* **4.2 DOSE AND METHOD OF ADMINISTRATION – Hepatic impairment 5.2 PHARMACOKINETIC PROPERTIES – Hepatic impairment**.

**Use in the elderly**

No data available. See **4.2 DOSE AND METHOD OF ADMINISTRATION – Dosage in Type 1 Gaucher Disease - children, adolescents and the elderly.**

**Paediatric use**

See **4.2 DOSE AND METHOD OF ADMINISTRATION** – Dosage in Niemann-Pick type C disease - Children and **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE** - Niemann-Pick type C disease - Growth events in paediatric and adolescent patients.

**Effects on laboratory tests**

No data available.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

*In vitro* data demonstrated that miglustat had no relevant inhibitory effect on the cytochrome P450 (CYP) isoenzymes evaluated (CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4). Consequently, miglustat is not expected to increase the plasma concentrations of medicinal products which are metabolised by these isoenzymes.

Limited pharmacokinetic data suggest that co-administration of ZAVESCA® and imiglucerase rch (Cerezyme®) in patients with Type 1 Gaucher disease may result in decreased exposure to miglustat (a reduction of approximately 22% and 14% was observed in $C_{max}$ and AUC, respectively, in a small parallel-group study).

A population pharmacokinetic analysis indicated that loperamide has no effect on the pharmacokinetics of miglustat.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

**Effects on fertility**

***Male Fertility***

Studies in the rat have shown that miglustat adversely affects spermatogenesis, sperm parameters (in particular, increases in the number of abnormal sperm) and reduces fertility.

**Use in pregnancy**

**Pregnancy Category D**

There is currently no relevant experience with the administration of ZAVESCA® in pregnant women. Miglustat might be expected to cross the placenta and studies in animal have shown maternal and embryo-fetal toxicity, including decreased embryo-fetal survival. Observed effects included increased post-implantation losses, and decreases in fetal body weights and ossification of various bones. There was an increase incidence of vascular anomalies in rabbits. Increased gestation length and prolonged parturition were observed in rats. Increased post-implantation loss and an increase in gestation length were observed at doses of ≥60 mg/kg/day in rats (relative exposure based on plasma AUC of 1 compared to AUC expected at the maximum recommended clinical dose). Prolonged parturition was observed at 180 mg/kg/day (relative exposure of 3 based on AUC at the maximum recommended clinical dose). In rabbits, prolonged parturition was reported, increased post-implantation losses were observed at doses

of ≥45 mg/kg/day, and the increase in vascular abnormalities occurred at ≥15 mg/kg/day (relative exposure on a body surface area basis of <1 in both instances). In general, reproductive toxicity was observed at doses that were maternotoxic. ZAVESCA® should not be used during pregnancy.

**Contraception**

Effective contraceptive measures should be used by women of child-bearing potential. Reliable contraceptive methods should be maintained whilst male patients are taking ZAVESCA® and for 3 months following discontinuations.

**Use in lactation**

It is not known if miglustat is excreted in breast milk. ZAVESCA® should not be used during breastfeeding.

## 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

**Clinical studies**

In 11 clinical trials in different indications 247 subjects were treated with ZAVESCA® at dosages of 50-200 mg up to 3 times daily (tid) for a median duration of 2.0 years. Of these subjects, 132 had type 1 Gaucher disease, and 40 had Niemann-Pick type C disease. The most common adverse reactions were gastrointestinal, with diarrhoea and other abdominal complaints, and weight loss.

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

**GAUCHER DISEASE TYPE 1:***

***Adverse reactions based on 132 patients in clinical trials***

***Blood and lymphatic system disorders***
Common: Thrombocytopenia, anaemia, splenomegaly

***Metabolism and nutrition disorders***
Common: Decreased appetite

***Psychiatric disorders***
Common: Insomnia

***Nervous system disorders***
Very common: Tremor, headache
Common: Paraesthesia, dizziness, hypoaesthesia, peripheral neuropathy, amnesia, coordination abnormal, disturbance in attention, memory impairment, migraine

***Gastrointestinal disorders***
Very common: Diarrhoea, flatulence, abdominal pain, abdominal pain upper

Common: Nausea, abdominal distension/discomfort, vomiting, constipation, dyspepsia, gastrointestinal pain, dry mouth, gastritis

***Musculoskeletal and connective tissue disorders***
Common: Muscle spasms, muscular weakness, arthralgia, bone pain

***General disorders and administration site conditions***
Common: Fatigue, asthenia, chills, malaise, chest pain, feeling jittery

***Ear and Labyrinth Disorders***
Common: Vertigo

***Eye Disorders***
Common: Vision blurred

***Hepatobiliary Disorders***
Common: Hepatomegaly

***Investigations***
Very Common: Weight decreased
Common: Chitotriosidase increased, platelet count decreased, haemoglobin decreased, angiotensin converting enzyme increased, haematocrit decreased

**NIEMANN-PICK TYPE C:***

***Adverse reactions based on 40 patients in clinical trials***

***Metabolism and nutrition disorders***
Very common: Decreased appetite
Common: Lactose intolerance

***Psychiatric disorders***
Common: Depression, tearfulness

***Nervous system disorders***
Very common: Tremor
Common: Paraesthesia, lethargy, headache, amnesia, ataxia, axonal neuropathy, dysarthria, polyneuropathy

***Gastrointestinal disorders***
Very common: Diarrhoea, flatulence, abdominal pain, abdominal pain upper, abdominal distension/discomfort, vomiting
Common: Nausea, eructation, haemorrhagic diarrhoea, faecal incontinence

***General disorders and administration site conditions***
Common: Fatigue, energy increased, thirst

***Skin and subcutaneous tissue disorders***
Common: Rash maculo-papular

***Infections and Infestations***
Common: Gastroenteritis

***Renal and urinary disorders***
Common: Pollakiuria

***Investigations***
Very Common: Weight decreased, nerve conduction studies abnormal

Weight loss, reported as "weight decreased", has been observed in 52.3% of subjects with Type 1 Gaucher Disease and in 60.0% of patient with Niemann-Pick Type C disease.

ZAVESCA® has been studied in several diseases including Type 1 Gaucher disease and Niemann-Pick type C disease where certain events reported as ADRs such as neurological symptoms/signs and thrombocytopenia could also be due to the underlying condition.

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

**Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

## 4.9 OVERDOSE

No acute symptoms of overdose have been identified. ZAVESCA® has been administered at doses of up to 3,000 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 doses of 800 mg/day or higher dose.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 PHARMACODYNAMIC PROPERTIES

**Mechanism of Action**

***Type 1 Gaucher disease***

Type 1 Gaucher disease is an inherited metabolic disorder caused by a functional deficiency of β-glucocerebrosidase, the enzyme that mediates the degradation of the glycosphingolipid; glucocerebroside. The failure to degrade glucocerebroside results in the lyosomal storage of this material within tissue macrophages, leading to widespread pathology. Macrophages containing stored glucocerebroside are typically found in the liver, spleen, and bone marrow and occasionally in lung, kidney and intestine. Secondary haematogical consequences include severe anaemia and thrombocytopenia in addition to the characteristic progressive hepatosplenomegaly. Skeletal complications include osteonecrosis and osteopenia with secondary pathological fractures and associated pain; all of which can cause significant morbidity.

Miglustat acts as a competitive and reversible inhibitor of glucosylceramide synthase, the enzyme responsible for the first and committed step in the synthesis of most glycosphingolipids. The goal of treatment with miglustat is to reduce the rate of glycosphingolipid biosynthesis so that the amount of glycosphingolipid is reduced to a level which allows the residual activity of the deficient glucocerebrosidase enzyme to be more effective (substrate reduction therapy).

*In vitro* and *in vivo* studies have shown that miglustat can reduce the synthesis of glucosylceramide-based glycosphingolipids in a dose-dependent manner

### *Niemann-Pick type C (NP-C) disease*

NP-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 abnormal accumulation of glycosphingolipids in neurons and glial cells.

Miglustat showed efficacy in relevant animal models of NP-C disease and resulted in a delayed onset of neurological dysfunction (ataxia and intention tremor), an increase in the average life span and reduction in ganglioside accumulation and accompanying neuropathological changes.

## Clinical trials

### *Type 1 Gaucher disease*

The safety and efficacy of ZAVESCA® in Type 1 Gaucher disease has been investigated to date in three open-label, non-comparative studies and in one randomised active-controlled open label study which included an open extension period of up to 24 months. Efficacy parameters included the evaluation of liver and spleen volume, haemoglobin concentration and platelet count.

In the three non-comparative, monotherapy studies of ZAVESCA®, all patients had mild to moderate Type 1 Gaucher disease, who were unable or unwilling to receive enzyme replacement therapy (ERT), or who had not taken ERT in the preceding 3 months. Mild to moderate Type 1 Gaucher disease was defined as measurable liver or spleen enlargement and Hb<115g/L or platelets <100 x $10^9$/L; if splenectomised, liver weight should be >2.5% body weight.

A brief overview of the design and outcome of each of these studies is provided below.

*Study 1*

In Study 1, ZAVESCA® was administered at a dose of 100 mg, three times daily (t.i.d.). Twenty-eight patients were enrolled in the study, of whom 22 patients completed the initial 12 month phase and 14 patients completed 24 months of treatment. Compared with baseline values, there were statistically significant reductions in hepato- and splenomegaly (measured by magnetic resonance imaging or computed tomography) (Table 1).

*Study 2*

In Study 2, ZAVESCA® was administered at a dose of 50 mg t.i.d. for 6 months in a total of 18 adult patients. Seventeen patients completed the study. Sixteen patients elected to continue to receive ZAVESCA® in a 6-month extended treatment protocol and 12 patients continued treatment up to 12 months (see Table 1 for a summary of efficacy results).

*Study 3*

In Study 3, ZAVESCA® was administered at a dose of 100 mg t.i.d. for 12 months, with an optional extended study period of 12 months for a total of 24 months. Eight patients were enrolled in the study, of which 7 patients completed both the initial 12 month phase and the extension up to 24 months (see Table 1 for a summary of efficacy results).

**Table 1: Miglustat efficacy in mild to moderate Type 1 Gaucher disease**

| | 6 months | 1 year | 2 years |
|---|---|---|---|
| ***Study 1 – 100 mg tid*** | | | |
| | (n=21) | (n=21) | (n=12) |
| Liver volume mean Baseline, L | 2.4 | 2.4 | 2.5 |
| % change | -7.0 | -12.1 | -14.5 |
| [95% CI] | [-10.5, -3.4] | [-16.4, -7.9] | [-19.3, -9.7] |
| | (n=18)* | (n=18)* | (n=10)* |
| Spleen volume mean Baseline, L | 1.6 | 1.6 | 1.6 |
| % change | -15.1 | -19.0 | -26.4 |
| [95% CI] | [-18.4, -11.8] | [-23.7, -14.3] | [-30.4, -22.4] |
| | (n=22) | (n=22) | (n=13) |
| Haemoglobin mean Baseline, g/L | 119 | 119 | 110 |
| Change (g/L) | 0.3 | 3 | 9 |
| [95% CI] | [-2, 2] | [-1, 6] | [3, 15] |
| | (n=22) | (n=22) | (n=13) |
| Platelets mean Baseline, $x10^9$/L | 77 | 77 | 72 |
| Change ($x10^9$/L ) | 4 | 8 | 14 |
| [95% CI] | [-1, 9] | [2, 15] | [8, 19] |
| ***Study 2 – 50 mg tid*** | | | |
| | (n=17) | (n=13) | N.D. |
| Liver volume mean Baseline, L | 2.5 | 2.4 | |
| % change | -5.9 | -6.2 | |
| [95% CI] | [-9.9, -1.9] | [-12.0, -0.5] | |
| | (n=11)** | (n=9)†† | N.D. |
| Spleen volume mean Baseline, L | 2.0 | 2.0 | |
| % change | -4.5 | -10.1 | |
| [95% CI] | [-8.2, -0.7] | [-20.1, -0.1] | |
| | (n=17) | (n=13) | N.D. |
| Haemoglobin mean Baseline, g/L | 116 | 119 | |
| Change (g/L) | -1 | 1 | |
| [95% CI] | [-5, 2] | [-7, 9] | |
| | (n=17) | (n=13) | N.D. |
| Platelets mean Baseline, $x10^9$/L | 116 | 122 | |
| Change ($x10^9$/L) | 5 | 14 | |
| [95% CI] | [-6, 17] | [-3, 31] | |
| ***Study 3 – 100 mg tid*** | | | |
| | (n=8) | (n=7) | (n=7) |
| Liver volume mean Baseline, L | 2.3 | 2.3 | 2.3 |
| % change | -8.4 | -9.4 | -5.6 |

| | 6 months | 1 year | 2 years |
|---|---|---|---|
| [95% CI] | [-16.1, 0.7] | [-19.5, 0.6] | [-12.1, 1.0] |
| | (n=8) | (n=7) | (n=7) |
| Spleen volume mean Baseline, L | 1.1 | 1.1 | 1.1 |
| % change | -19.0 | -14.4 | -15.4 |
| [95% CI] | [-30.4, -7.6] | [-31.9, 3.1] | [-34.4, 3.5] |
| | (n=8) | (n=7) | (n=7) |
| Haemoglobin mean Baseline, g/L | 132 | 132 | 132 |
| Change (g/L) | 2 | 0 | -3 |
| [95% CI] | [-6, 9] | [-5, 5] | [-9, 5] |
| | (n=8) | (n=7) | (n=7) |
| Platelets mean Baseline, $x10^9$/L | 84 | 84 | 84 |
| Change (($x10^9$/L) | 4 | 14 | 21 |
| [95% CI] | [-4, 13] | [2, 26] | [-30, 73] |

* 3 splenectomised. ** 7 splenectomised. †† 5 splenectomised.

*Study 4*

An 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. Patients who received ZAVESCA® in the randomised comparison period therefore received ZAVESCA® treatment for up to 24 months.

In the first 6 months in patients who were switched to ZAVESCA® monotherapy, 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. Analysis of 24-month ZAVESCA® monotherapy efficacy was conducted in 31 subjects who had received at least one dose of ZAVESCA®, who had a baseline value and at least one post-baseline assessment for liver and spleen, hemoglobin or platelets (Table 2). Mean liver and spleen volume did not increase after switching from Cerezyme® to ZAVESCA® monotherapy. Small decreases (<0.5 g/dL at the majority of timepoints) of mean haemoglobin concentration were observed after baseline, which were statistically significant at Months 6, and 12 of ZAVESCA® treatment. A small statistically significant decrease of mean platelet count from baseline was observed upon switching from Cerezyme® to ZAVESCA® monotherapy. One subject had low platelets reported as being clinically significant at any time and this subject already had low platelets at baseline.

No patient showed rapid deterioration of type 1 Gaucher disease following the switch to ZAVESCA® monotherapy

**Table 2*:* Active-controlled study of ZAVESCA® maintenance efficacy in Type 1 Gaucher disease**

| | Baseline | 6 months | 12 months | 18 months | 24 months |
|---|---|---|---|---|---|
| ***Study 4*** | | | | | |
| Liver volume mean, L | n=29<br>1.78 | n=27<br>1.78 | n=8<br>1.58 | n=9<br>2.04 | n=5<br>1.47 |
| Actual mean change, L (%)<br>95% CI of % change<br>p-value* | | -0.041(-1.69)<br>-5.75, 2.37<br>0.401 | -0.013(-0.75)<br>-6.14, 4.64<br>0.751 | -0.091(-3.89)<br>-9.78, 2.01<br>0.167 | -0.057(-2.68)<br>-14.09, 8.73<br>0.550 |
| Spleen volume mean, L | n=20<br>0.664 | n=21<br>0.856 | n=6<br>0.522 | n=6<br>0.735 | n=4<br>0.463 |
| Actual mean change, L (%)<br>95% CI of % change<br>p-value* | | 0.024 (3.32)<br>-5.75, 2.37<br>0.386 | -0.047 (-6.13)<br>-6.14, 4.64<br>0.064 | 0.019 (-0.10)<br>-9.78, 2.01<br>0.981 | -0.023 (-0.79)<br>-14.09, 8.73<br>0.926 |
| Haemoglobin mean, g/dL | n=31<br>12.75 | n=29<br>12.40 | n=28<br>12.38 | n=20<br>12.76 | n=6<br>12.97 |
| Actual mean change, g/dL (%)<br>95% CI of % change<br>p-value* | | -0.32 (-2.14)<br>-4.23, -0.04<br>0.046 | -0.36 (-2.48)<br>-4.64, -0.31<br>0.027 | -0.24 (-1.63)<br>-5.22, 1.97<br>0.356 | 0.20 (1.49)<br>-4.08, 7.05<br>0.523 |
| Platelets mean x109/L | n=31<br>171.7 | n=29<br>147.6 | n=28<br>146.6 | n=20<br>153.2 | n=6<br>14.2 |
| Actual mean change $x10^9$/L (%)<br>95% CI of % change<br>p-value* | | -22.5 (-12.0)<br>-17.4, -6.6<br><0.001 | -27.8 (-14.8)<br>-20.6, -9.0<br><0.001 | -33.0 (-16.9)<br>-25.2, -8.68<br><0.001 | -19.2 (-7.8)<br>-28.4, -12.8<br>0.376 |

* paired t-test on the percent change
All timepoints were determined from the efficacy baseline, which was defined as the visit from where Cerezyme® treatment was withdrawn.

Bone manifestations of type 1 Gaucher disease were evaluated in 3 open-label clinical studies (Studies 1, 3 and 4) 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 27/47 (57%) and 28/43 (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 (NP-C) disease*

Data to support safety and efficacy of ZAVESCA® in Niemann-Pick type C disease come from a prospective open-label clinical trial (OGT 918-007) and a retrospective survey. The clinical trial included 29 adult and juvenile patients in a 12-month controlled period, followed by extension treatment for an average 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.

The efficacy variable of primary interest in study OGT 918-007 was the change from baseline to Month 12 and last value in Horizontal Saccade Eye Movements α (HSEM-α), derived from the quantitative measurement of horizontal saccadic eye movement (SEM) velocity, using blinded, centralised assessment. The measure of saccadic eye movement was selected

because supranuclear gaze palsy (saccadic initiation failure) is often the earliest neurological sign in NP-C and because saccadic eye movement failure is associated with definite visual, learning and social handicap. There were no statistically significant differences between the ZAVESCA® and the No Treatment groups (see Table 3).

**Table 3: Analysis of change from baseline in HSEM-α (efficacy set Main Study Juveniles/Adults)**

| Parameter | | Adjusted mean change from baseline | | Estimated treatment difference | 95% CI | p-value |
|---|---|---|---|---|---|---|
| HSEM-α (ms/deg) | | ZAVESCA® | No Treatment | | | |
| | Month 12 | –0.329 | –0.055 | –0.274 | (–0.959, 0.411) | 0.414 |
| | Last value | –0.376 | –0.050 | –0.326 | (–1.000, 0.348) | 0.327 |

The ANCOVA model used for all analyses includes terms for baseline, age and treatment group, CI = confidence interval
Greater mean decreases in HSEM-α (i.e., improvements) from baseline to Month

A qualitative examination of the main sequences scatter plots and visual comparison of the regression slopes for the plots of saccades from 26 patients who provided useable data at both baseline and month 12 (or last visit) showed in the ZAVESCA® group, 15/19 patients (79%) were stable or improved (7 improved, 8 no change), 2 deteriorated, and 2 had ambiguous results while in the No treatment group, 2/7 patients (29%) were stable or improved (1 improved, 1 with no change), 3 deteriorated, and 2 had ambiguous results.

An additional exploratory analysis excluding patients on confounding benzodiazepine medication (a sedative that can slow saccades) demonstrated a significant difference in HSEM-α between treatment groups at 12 months (see Table 4)

**Table 4: HSEM-α: Analyses of changes from baseline to last value (Efficacy set) – OGT 918-007 Main study, Comparative Phase**

| HSEM-α (ms/deg) | Adjusted mean change from baseline | | Estimated treatment difference | 95% confidence interval | p-value |
|---|---|---|---|---|---|
| | ZAVESCA® | No Treatment | | | |
| Planned analysis[a] | | | | | |
| Last value | –0.376 | –0.050 | –0.326 | –1.000, 0.348 | 0.327 |
| Including center in the model[b] | | | | | |
| Last value | –0.463 | 0.055 | –0.518 | –1.125, 0.089 | 0.091 |
| Excluding pts on benzodiazepines[c] | | | | | |
| Last value | –0.485 | 0.234 | –0.718 | –1.349, –0.088 | 0.028 |

[a] The ANCOVA model used includes terms for baseline, age, and treatment group.
[b] The ANCOVA model used includes terms for baseline, centre, and treatment group.
[c] The ANCOVA model used includes terms for baseline, centre, and treatment group. Seven patients received benzodiazepines during the study (6 in the miglustat group, and 1 in the No Treatment group) and were excluded from this analysis.
ANCOVA = analysis of covariance, HSEM = horizontal saccadic eye movement, pts = patients.

Secondary efficacy endpoints: Swallowing function, motor disability, and cognitive ability were also assessed. Swallowing function was assessed on a rating scale, evaluating the patient's ability to swallow water and food substances of varying consistencies. The observed relative risk for any deterioration of swallowing function up to Month 12 with ZAVESCA® vs. No treatment was 0.4 (95% CI 0.13, 1.22, p = 0.17).

Motor disability was assessed with the Hauser Standard Ambulation Index (SAI). The observed mean increase (deterioration) in SAI from Baseline to Month 12 was smaller with ZAVESCA® treatment versus No treatment [ZAVESCA®: 0.087 (95% CI -0.287, 0.461), No Treatment: 0.802 (95% CI 0.220, 1.385), treatment effect (ANCOVA with terms for baseline, center, treatment group): -0.715 (95% CI -1.438, 0.007, p= 0.052)].

The assessment of cognitive ability, measured through change from baseline to Month 12 in the Folstein Mini-Mental Status Examination (MMSE) score in adult/adolescent patients, showed a difference in favour of ZAVESCA® [ZAVESCA®: 1.219 (95% CI -0.060, 2.498), No Treatment: -0.352 (95% CI -2.213, 1.510), treatment effect (ANCOVA with terms for baseline, center, treatment group): -1.571 (95% CI -0.692, 3.834, p= 0.165)].

Several other secondary and exploratory endpoints did not indicate clinically relevant effects of ZAVESCA® vs. No Treatment. These included other measures of saccadic eye movements, liver, spleen and cerebellar volumes, standardized neurological examination, additional neuropsychological tests, and quality of life measures. The data from treatment with ZAVESCA® of paediatric patients with Niemann-Pick Type C disease corroborated the findings in the controlled study in adolescent and adult patients.

In the retrospective survey, disease progression was assessed within the functional domains swallowing, ambulation, manipulation (dysmetria/dystonia), language function/articulation, and overall disability according to a published NP-C disability scale. Across functional domains and for overall disability, ZAVESCA® treatment was associated with clinically relevant reductions in annualized progression rate, compared with pre-treatment.

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®.

## 5.2 PHARMACOKINETIC PROPERTIES

Pharmacokinetic parameters of miglustat were assessed in healthy subjects, in a small number of patients with Type 1 Gaucher disease, and in adults, adolescents and children with Niemann-Pick type C disease.

Miglustat, dosed at 50 and 100 mg in Gaucher patients, exhibits dose proportional pharmacokinetics. The pharmacokinetics were not altered after repeated dosing, three times daily, for up to 12 months.

The kinetics of miglustat appear to be dose linear and time independent.

### Absorption

In healthy subjects miglustat is rapidly absorbed. After a 100 mg oral dose, maximum plasma concentrations are reached approximately 2 hours after dosing. Absolute bioavailability has not been determined. The effective half-life of miglustat is approximately 6 to 7 hours, which predicts that steady-state will be achieved by 1.5 to 2 days following the start of three times daily dosing. Food may delay the absorption of miglustat. It is recommended that miglustat be taken away from food to reduce gastrointestinal effects (*see* **4.2 DOSE AND METHOD OF ADMINISTRATION**).

### Distribution

The apparent volume of distribution of miglustat is 83L. Miglustat does not bind to plasma proteins. Miglustat crosses the blood-brain barrier.

### Metabolism and Excretion

The major route of excretion of miglustat is renal with a mean of 82.8% of an administered dose recovered in the urine. Faecal excretion accounted for a mean of 11.9% of the dose. The

majority of the material excreted was unchanged miglustat. Minor metabolites were detected in plasma, urine, and faeces. Apparent oral clearance (CL/F) is 230 ± 39 mL/min. The apparent terminal half-life is 6-7 hours.

The pharmacokinetics of miglustat are 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 Niemann-Pick type C disease aged 5-11 years. Dosing in these children at 200 mg t.i.d. adjusted for body surface area resulted in $C_{max}$ and $AUC_{\tau}$ values which were not appreciably different to those in adolescent/adult patients on 200 mg t.i.d (see Table 5).

**Table 5: Comparative Pharmacokinetics in healthy and disease states**

| Parameters - geometric mean (CV) | NP-C<br>200mg TID<br>N=6 Age >12 y | Type 1 Gaucher<br>100 mg TID<br>N=5 Age >12 y | Healthy volunteers 100mg OD |
|---|---|---|---|
| $AUC_{(0\text{-}8h)}$ (ng.h/mL) | 16412 (19.5) | 9071[b] (24) | 10622[a] |
| $C_{max}$ (ng/mL) | 2698 (22.9) | 1722 (19) | 1367 (24.6) |
| $C_{trough}$ (ng/mL) | 1427 (18.3) | | |
| $T_{max}$ - medium (h)<br>(range) | 3.00 (0.75 - 4) | 1 (1-4) | 2.5 (1-4) |

a AUC 0-1h

b AUC 0 - 6 to 8h

## Special populations

Over the range of data available, no significant relationships or trends were noted between miglustat pharmacokinetic parameters and demographic variables (e.g. age, body mass index, gender or ethnicity).

### *Elderly (70 years and older)*

There are currently no pharmacokinetic data available in the elderly (>70 years).

### *Renal impairment*

Renal impairment has a significant effect on the pharmacokinetics of miglustat with an increased systemic exposure associated with a decrease in CL/F, based on observations in patients with Fabry disease and renal insufficiency. These data suggest an approximate decrease in CL/F of 40% and 60%, in mild and moderate renal impairment, respectively. Only very limited data are available in severe renal impairment.

### *Hepatic impairment*

No data are available to evaluate the effects of hepatic impairment on miglustat pharmacokinetics. However, as miglustat is eliminated primarily via the kidneys it is not expected that hepatic impairment will have a clinically relevant effect on the pharmacokinetics of miglustat.

## 5.3 PRECLINICAL SAFETY DATA

**Genotoxicity**

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

**Carcinogenicity**

In a 2 year carcinogenicity study in rats, miglustat increased the incidence of Leydig cell tumours at all dose levels studied (30-180 mg/kg/day). Based on plasma AUC comparison, the lowest dose represents a relative exposure of only about 0.4 of that expected at the maximum recommended clinical dose. The mechanism of tumour induction and the relevance of these tumours to human risk assessment are unknown, but Leydig cell tumours can occur in male rats by a non-genotoxic mechanism involving hormonal modulation of testosterone synthesis. The carcinogenic response seen in rats occurred at dose levels which also produced testicular tubular atrophy.

In a 2 year oral carcinogenicity study in mice, miglustat increased the incidence of inflammatory lesions, hyperplasia and tumours (mainly adenocarcinomas) in the large intestine at all doses tested (210, 420 and 840/500 mg/kg/day (dose reduction after half a year)). Exposure to miglustat (mg/kg) was 18-42 times that at the maximal recommended clinical dose. The relevance of these tumors to humans on long term ZAVESCA® therapy cannot be excluded.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

Inactives: sodium starch glycollate, povidone, magnesium stearate

Capsule shell: empty hard gelatin capsules size 4 white Op.44.000/44.000 pure bovine (ARTG PI No 108031)

Printing ink: OPACODE monogramming ink S-1-277002 BLACK (ARTG PI No 107581), OPACODE monogramming ink S-1-27794 BLACK (ARTG PI No 12104) or TekPrint SW-9008 Black Ink (ARTG PI No 2328)

## 6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

## 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

## 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C

## 6.5 NATURE AND CONTENTS OF CONTAINER

ZAVESCA® (miglustat 100mg) is available in blister cartons of 90 hard gelatin capsules

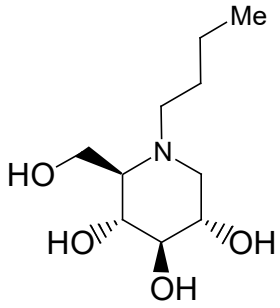
## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

## 6.7 PHYSICOCHEMICAL PROPERTIES

Miglustat is an orally active, non-peptide, N-alkylated imino sugar, which is a synthetic analogue of D-glucose. It is a white to off-white crystalline solid and is highly water soluble (›1000mg/mL as a free base). The chemical name of miglustat is 1, 5-(butylimino)-1,5-dideoxy-D-glucitol.

**Chemical structure**




Molecular formula: $C_{10}H_{21}NO_4$

Molecular mass: 219.28

**CAS number**

72599-27-0

# 7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4)

# 8 SPONSOR

JANSSEN-CILAG Pty Ltd

1-5 Khartoum Rd

Macquarie Park NSW 2113 Australia

Telephone: 1800 226 334

NZ Office: Auckland New Zealand

# 9 DATE OF FIRST APPROVAL

10 Feb 2011

# 10 DATE OF REVISION

20 November 2024

## SUMMARY TABLE OF CHANGES

| Section Changed | Summary of new information |
|---|---|
| **4.4** | Update to include Crohn's disease |