
ZAVESCA[®]
Miglustat
100 mg capsules
AUSTRALIAN PRODUCT INFORMATION

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 ADMINISTRATION

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.

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 should be adjusted on the basis of body surface area (BSA, mg/m²) as illustrated below:

BSA (m²)*	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 (m²) = 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 (GD1 and NP-C)

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/1.73m², 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 m², 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 m²) is not recommended owing to a lack of clinical experience.

Hepatic impairment (GD1 and NP-C)

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 10⁹/L and active bone disease. Enzyme replacement therapy remains the standard of care for previously untreated patients with Type 1 Gaucher disease.

Neurological Events

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 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. 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.

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

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 B₁₂ 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.

Diarrhoea

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. 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 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

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 events 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**). 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 m²) and thus, ZAVESCA[®] is not recommended in these patients.

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 Type 1 Gaucher Disease - children, adolescents and the elderly 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 (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

Male patients should maintain reliable contraceptive methods whilst taking ZAVESCA® and for 3 months thereafter. 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 has been shown to be embryotoxic when administered to rats and rabbits. 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 dystocia 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). Dystocia was observed at 180 mg/kg/day (relative exposure of 3 based on AUC at the maximum recommended clinical dose). In rabbits, 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. Effective contraceptive measures should be used by women of childbearing potential.

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 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. Adverse events reported in clinical trials of ZAVESCA® in 90 patients with Type 1 Gaucher disease and in 40 patients with Niemann-Pick type C disease are listed below by body system and frequency (very common: $> 1/10$, common $> 1/100$ and $< 1/10$). Most events were of mild to moderate severity.

Blood and lymphatic system disorders

Common: Thrombocytopenia

Metabolism and nutrition disorders

Very common: Weight loss

Common: Anorexia, Decreased appetite

Psychiatric disorders

Common: *Insomnia, libido decreased*

Nervous system disorders

Very common: Tremor

Common: Peripheral neuropathy, headache, dizziness, paraesthesia, hypoesthesia, ataxia

Gastrointestinal disorders

Very common: Diarrhoea, flatulence, abdominal pain,

Common: Nausea, constipation, vomiting, dyspepsia, abdominal distension/discomfort

Musculoskeletal and connective tissue disorders

Common: Muscle spasms

General disorders and administration site reactions

Common: Fatigue, asthenia

Investigations

Common: Nerve conduction studies abnormal

Weight loss has been observed in approximately 60% of patients. The peak was at 12 months with a mean weight loss of 6-7% of body weight and a subsequent trend for the weight to return to baseline levels thereafter.

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 \geq 800 mg/day.

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 lysosomal 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 haematological 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 10⁹/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			
Liver volume mean Baseline, L	(n=21) 2.4	(n=21) 2.4	(n=12) 2.5
% change	-7.0	-12.1	-14.5
[95% CI]	[-10.5, -3.4]	[-16.4, -7.9]	[-19.3, -9.7]
Spleen volume mean Baseline, L	(n=18)* 1.6	(n=18)* 1.6	(n=10)* 1.6
% change	-15.1	-19.0	-26.4
[95% CI]	[-18.4, -11.8]	[-23.7, -14.3]	[-30.4, -22.4]
Haemoglobin mean Baseline, g/L	(n=22) 119	(n=22) 119	(n=13) 110
Change (g/L)	0.3	3	9
[95% CI]	[-2, 2]	[-1, 6]	[3, 15]
Platelets mean Baseline, x10 ⁹ /L	(n=22) 77	(n=22) 77	(n=13) 72
Change (x10 ⁹ /L)	4	8	14
[95% CI]	[-1, 9]	[2, 15]	[8, 19]
Study 2 – 50 mg tid			
Liver volume mean Baseline, L	(n=17) 2.5	(n=13) 2.4	N.D.
% change	-5.9	-6.2	
[95% CI]	[-9.9, -1.9]	[-12.0, -0.5]	

	6 months	1 year	2 years
Spleen volume mean Baseline, L	(n=11)** 2.0	(n=9)†† 2.0	N.D.
% change	-4.5	-10.1	
[95% CI]	[-8.2, -0.7]	[-20.1, -0.1]	
Haemoglobin mean Baseline, g/L	(n=17) 116	(n=13) 119	N.D.
Change (g/L)	-1	1	
[95% CI]	[-5, 2]	[-7, 9]	
Platelets mean Baseline, x10 ⁹ /L	(n=17) 116	(n=13) 122	N.D.
Change (x10 ⁹ /L)	5	14	
[95% CI]	[-6, 17]	[-3, 31]	
Study 3 – 100 mg tid			
Liver volume mean Baseline, L	(n=8) 2.3	(n=7) 2.3	(n=7) 2.3
% change	-8.4	-9.4	-5.6
[95% CI]	[-16.1, 0.7]	[-19.5, 0.6]	[-12.1, 1.0]
Spleen volume mean Baseline, L	(n=8) 1.1	(n=7) 1.1	(n=7) 1.1
% change	-19.0	-14.4	-15.4
[95% CI]	[-30.4, -7.6]	[-31.9, 3.1]	[-34.4, 3.5]
Haemoglobin mean Baseline, g/L	(n=8) 132	(n=7) 132	(n=7) 132
Change (g/L)	2	0	-3
[95% CI]	[-6, 9]	[-5, 5]	[-9, 5]
Platelets mean Baseline, x10 ⁹ /L	(n=8) 84	(n=7) 84	(n=7) 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 1.78	n=27 1.78	n=8 1.58	n=9 2.04	n=5 1.47
Actual mean change, L (%)		-0.041(-1.69)	-0.013(-0.75)	-0.091(-3.89)	-0.057(-2.68)
95% CI of % change		-5.75, 2.37	-6.14, 4.64	-9.78, 2.01	-14.09, 8.73
p-value*		0.401	0.751	0.167	0.550
Spleen volume mean, L	n=20 0.664	n=21 0.856	n=6 0.522	n=6 0.735	n=4 0.463
Actual mean change, L (%)		0.024 (3.32)	-0.047 (-6.13)	0.019 (-0.10)	-0.023 (-0.79)
95% CI of % change		-5.75, 2.37	-6.14, 4.64	-9.78, 2.01	-14.09, 8.73
p-value*		0.386	0.064	0.981	0.926
Haemoglobin mean, g/dL	n=31 12.75	n=29 12.40	n=28 12.38	n=20 12.76	n=6 12.97
Actual mean change, g/dL (%)		-0.32 (-2.14)	-0.36 (-2.48)	-0.24 (-1.63)	0.20 (1.49)
95% CI of % change		-4.23, -0.04	-4.64, -0.31	-5.22, 1.97	-4.08, 7.05
p-value*		0.046	0.027	0.356	0.523
Platelets mean x10 ⁹ /L	n=31 171.7	n=29 147.6	n=28 146.6	n=20 153.2	n=6 14.2
Actual mean change x10 ⁹ /L (%)		-22.5 (-12.0)	-27.8 (-14.8)	-33.0 (-16.9)	-19.2 (-7.8)
95% CI of % change		-17.4, -6.6	-20.6, -9.0	-25.2, -8.68	-28.4, -12.8
p-value*		<0.001	<0.001	<0.001	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

HSEM- α (ms/deg)	Adjusted mean change from baseline		Estimated treatment difference	95% confidence interval	p-value
	ZAVESCA [®]	No Treatment			
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_{τ} 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 200mg TID N=6 Age >12 y	Type 1 Gaucher 100 mg TID N=5 Age >12 y	Healthy volunteers 100mg OD
$AUC_{(0-8h)}$ (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) (range)	3.00 (0.75 - 4)	1 (1-4)	2.5 (1-4)

a AUC 0-1h

b AUC 0 - 6 to 8h

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.

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.

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

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: gelatin, titanium dioxide (E171), black printing ink

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

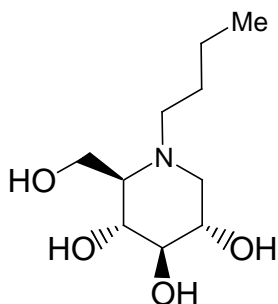
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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: C₁₀H₂₁NO₄

Molecular mass: 219.28

CAS number

72599-27-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

10 Feb 2011

10 DATE OF REVISION

24 April 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	PI reformat
3	Addition of pharmaceutical form information