SCHEDULING STATUS

Schedule 4

1. NAME OF THE MEDICINE

ZAVESCA, 100 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100 mg miglustat

Sugar free.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Capsule, hard

White capsules with “OGT 918” printed in black on the cap and “100” printed in black on the body. The capsule dimensions are 14,3 mm X 5,32 mm

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 medical practitioners who are knowledgeable in the management of Gaucher disease or Niemann-Pick type C disease, as appropriate.

Dosage in type 1 Gaucher disease

Adult

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

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

Paediatric population

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

Dosage in Niemann-Pick type C disease

Adult

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

Paediatric population

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

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

Body surface area	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.

Special populations

Elderly

There is no experience with the use of ZAVESCA in patients over the age of 70.

Renal impairment

Pharmacokinetic data indicate increased systemic exposure to miglustat in patients with renal impairment. In patients with an adjusted creatinine clearance of 50–70 mL min/1,73 m^2, administration should commence at a dose of 100 mg twice daily in patients with type 1 Gaucher disease and at a dose of 200 mg twice daily (adjusted for body surface area in patients below the age of 12) in patients with Niemann-Pick type C disease.

In patients with an adjusted creatinine clearance of 30–50 mL/min/1,73 m^2, administration should commence at a dose of 100 mg once daily in patients with type 1 Gaucher disease and at a dose of 100 mg twice daily (adjusted for body surface area in patients below the age of 12) in patients with Niemann-Pick type C disease. Use in patients with severe renal impairment (creatinine clearance < 30 mL/min/1,73 m^2) is not recommended (see sections 4.4 and 5.2).

Hepatic impairment

ZAVESCA has not been evaluated in patients with hepatic impairment.

Method of administration

ZAVESCA can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in "List of excipients"

4.4 Special warnings and precautions for use

Tremor

Approximately 37 % 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, and discontinuation of treatment could be considered by the treating practitioner.

Gastrointestinal disturbances

Gastrointestinal events, mainly diarrhoea, have been observed in more than 80 % of patients, either at the outset of treatment or intermittently during treatment (see section 4.8). The mechanism is most likely inhibition of intestinal disaccharidases such as sucrase-isomaltase in the gastrointestinal tract leading to reduced absorption of dietary disaccharides. In clinical practice, miglustat-induced gastrointestinal events have been observed to respond to individualised diet modification (for example reduction of sucrose, lactose and other carbohydrate intake), taking ZAVESCA between meals, and/or anti-diarrhoeal medicinal products. 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, such as inflammatory bowel disease.

Effects on spermatogenesis

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

Special populations

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 to miglustat is markedly increased in patients with severe renal impairment (see section 5.2). At present, there is insufficient clinical experience in these patients to provide dosing recommendations. Use of ZAVESCA in patients with severe renal impairment (creatinine clearance < 30 mL/min/1,73 m^2) is not recommended.

Type 1 Gaucher disease

Although no direct comparisons with Enzyme Replacement Therapy (ERT) have been performed in treatment-naive patients with type 1 Gaucher disease, there is no evidence of ZAVESCA having an efficacy or safety advantage over ERT. ERT remains 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.
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 together with neurodiagnostic assessments as needed.

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

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.

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 as clinically indicated.

Paediatric population

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

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breastfeeding

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

Fertility

Studies in the rat have shown that miglustat adversely affects sperm parameters (motility and morphology) thereby reducing fertility (see section 4.4). Until further information is available, it is advised that before seeking to conceive, male patients

should cease ZAVESCA and maintain reliable contraceptive methods for 3 months thereafter.

Contraceptive measures should be used by women of childbearing potential. Male patients should maintain reliable contraceptive methods while taking ZAVESCA (see section 4.4).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

In 11 clinical trials in different indications 247 patients were treated with ZAVESCA at dosages of 50-200 mg three times daily for an average duration of 2,1 years. Of these patients, 132 had type 1 Gaucher disease, and 40 had Niemann-Pick type C disease.

Adverse reactions were generally of mild to moderate severity and occurred with similar frequency across indications and dosages tested.

Tabulated list of adverse reactions

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

System organ class	Adverse reaction	Frequency
Blood and lymphatic system disorders	Thrombocytopaenia	Common
Metabolism and nutrition disorders	Weight loss, decreased appetite	Very common
Psychiatric disorders	Depression, insomnia, libido decreased	Common
Nervous system disorders	Tremor,	Very common

	Peripheral neuropathy, ataxia, amnesia, paraesthesia, hypoaesthesia, headache, dizziness	Common
Gastrointestinal disorders	Diarrhoea, flatulence, abdominal pain	Very common
	Nausea, vomiting, abdominal distension/discomfort, constipation, dyspepsia	Common
Musculoskeletal and connective tissue disorders	Muscle spasms, muscle weakness	Common
General disorders and administration site reactions	Fatigue, asthenia, chills and malaise	Common

Investigations	Nerve conduction studies abnormal	Common

Description of selected adverse reactions

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of

The medicine is important. It allows

continued monitoring of the benefit/risk balance of the medicine.

Health care providers are asked to report any suspected

adverse reactions to SAHPRA via:"6.04 Adverse Drug

Reactions Reporting Form", found online under SAHPRA's

publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms

No acute symptoms of overdose have been identified.

Adverse events observed at higher than recommended doses included granulocytopaenia, dizziness and paraesthesia, leukopaenia and neutropaenia.

Management

In case of overdose general symptomatic and supportive medical care is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A.32.16 Other

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 Enzyme Replacement Therapy (ERT). 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/L and a mean platelet count increase of 8,29 × 109/L were observed. Clinical benefit has been assessed at 24 and 36 months in 13 patients. After 3 years of continuous miglustat treatment, mean reductions in liver and spleen organ volume were 17,5 % and 29,6 %, respectively. There was a mean increase of 22,2 × 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 imiglucerase, imiglucerase in combination with miglustat, or switch to miglustat. This study was conducted over a 6 month randomised comparison period followed by 18 months extension where all patients received miglustat monotherapy. In the first 6 months in patients who were switched to miglustat, liver and spleen organ volumes and haemoglobin levels were unchanged. In some patients there were reductions in platelet count and increases in chitotriosidase activity indicating that miglustat monotherapy may not maintain the same control of disease activity in all patients. 29 patients continued in the extension period. When compared to the measurements at 6 months, disease control was unchanged after 18 and 24 months of miglustat monotherapy (20 and 6 patients, respectively). No patient showed rapid deterioration of type 1 Gaucher disease following the switch to miglustat monotherapy.

Niemann-Pick type C disease

A prospective open-label 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 sub-study 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 miglustat for more than 3 years.

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

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

5.2 Pharmacokinetic properties

Pharmacokinetic parameters of miglustat were assessed in 45 healthy subjects, in a small number of patients with type 1 Gaucher disease (82 patients), and in adults, adolescents (6 adults/adolescents 12-39 years of age) and 4 children (5-11 years of age) with Niemann-Pick type C disease.

Absorption

The kinetics of miglustat appears 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 (Cmax was decreased by 36 %

and tmax delayed 2 hours), but has no statistically significant effect on the extent of absorption of miglustat (AUC decreased by 14 %).

Distribution and biotransformation

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.

Elimination

Following administration of a single dose of 100 mg 14C-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.

Paediatric population

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 three times daily adjusted for body surface area resulted in

Cmax and AUC$_T$ values which were approximately two-fold those attained after 100 mg three times daily 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.

Renal Impairment

Limited data in patients with 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 increases, vacuolation of thyroid and pancreas, cataracts, nephropathy and myocardial changes in rats. These findings were considered to be secondary to debilitation.

Administration of miglustat to male and female Sprague-Dawley rats by oral gavage for 2 years at dose levels of 30, 60 and 180 mg/kg/day resulted in an increased incidence of testicular interstitial cell (Leydig cell) hyperplasia and adenomas in male rats at all dose levels. The systemic exposure at the lowest dose was below or comparable to that observed in humans (based on AUC0-∞) at the recommended human dose. A No Observed Effect Level (NOEL) was not established and the effect was not dose dependent.

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.

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.

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,

Titanium dioxide (E171).

Printing ink

Black iron oxide (E172)

Shellac

6.2 Incompatibilities

Not applicable

6.3 Shelf life

To be assigned

6.4 Special precautions for storage

Store at or below 30 °C.

Keep capsules in blister strip and blister strip in

outer carton until required for use.

Keep out of reach of children.

6.5 Nature and contents of container

Blister pack comprises of thermoformed Aclar UltRx 2000 adhesive laminated to opaque white PVC film pockets lidded with a child resistant plain hard–tempered aluminium foil, coated with heat seal lacquer and printed paper side.

Pack size: 21 capsules per blister strip and 4 blister strips per outer carton.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

49/32.16/0152

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 October 2021