PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] SANDOZ MIGLUSTAT

migLUstat capsules

capsules, 100 mg, oral

ATC Code: A16AX06

Glucosylceramide Synthase Inhibitor

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RECENT MAJOR LABEL CHANGES

4 Dosage and Administration, 4.2 Recommended Dose and Dose Adjustment	08/2022
7 Warnings and Precautions, Reproductive Health: Female and Male Potential	08/2022
7 Warnings and Precautions, 7.1.1 Pregnant Women	08/2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Sandoz Miglustat (miglustat) is indicated for:

- the treatment of adult patients with mild to moderate Type 1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option.
- slowing the progression of some of the neurological manifestations in adult and pediatric (4-17 years of age) patients with Niemann-Pick Type C disease.

1.1 Pediatrics

There is no experience with the use of miglustat in patients with type 1 Gaucher disease under the age of 18; therefore, Health Canada has not authorized this indication for pediatric use.

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of miglustat in pediatric patients aged 4 to 18 years with Niemann-Pick Type C disease has been established. However, patients below 4 years of age were not enrolled in the prospective study of miglustat in Niemann-Pick Type C disease. Therefore, Health Canada has authorized this indication for use in pediatric patients aged 4 to 18 only.

1.2 Geriatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

- Sandoz Miglustat is contraindicated in patients who are hypersensitive to miglustat or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Sandoz Miglustat is contraindicated in women who are or may become pregnant. If Sandoz Miglustat is administered to women of reproductive potential, they should be informed of the potential hazard to the foetus (see 7 WARNINGS AND PRECAUTIONS and 16 NON-CLINICAL TOXICOLOGY).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Dose selection may need to be adjusted for patients with mild or moderate renal impairment. Use in patients with severe renal impairment is not recommended.
- Due to teratogenic risk, pregnancy should be ruled out prior to administration (see 16 NON-CLINICAL TOXICOLOGY).
- Temporary dose reduction may be necessary in some patients because of diarrhea. The risk of diarrhea may be reduced if Sandoz Miglustat is taken between meals (see 7 WARNINGS AND PRECAUTIONS).
- The benefit to the patient of treatment with Sandoz Miglustat should be evaluated on a regular basis.
- ***Switching from enzyme replacement therapy to Sandoz Miglustat in Gaucher disease:*** Switching to Sandoz Miglustat should be considered only for patients who have had their disease well stabilized on enzyme replacement therapy.

4.2 Recommended Dose and Dosage Adjustment

Dosage in type 1 Gaucher Disease

Adults

The recommended dose for the treatment of patients with Type 1 Gaucher disease is one 100 mg capsule administered orally three times a day at regular intervals.

Temporary dose reduction to 100 mg once or twice a day may be necessary in some patients because of diarrhea or tremor (see 7 WARNINGS AND PRECAUTIONS, Gastrointestinal, Neurological).

Pediatrics (under 18 years of age)

Health Canada has not authorized this indication for pediatric use.

Dosage in Niemann-Pick Type C Disease

Adults and juvenile (12-17 years old)

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

Pediatrics (4-12 years of age)

Patients below 4 years of age were not enrolled in the prospective study of miglustat in Niemann-Pick Type C disease. Dosing in patients between the ages of 4 to 12 should be adjusted on the basis of body surface area (BSA, mg/m^2) as illustrated below:

Body Surface Area (m^2)	Recommended dose

> 1.25	200 mg three times a day
> 0.88 – 1.25	200 mg twice a day
> 0.73 – 0.88	100 mg three times a day
> 0.47 – 0.73	100 mg twice a day
≤ 0.47	100 mg once a day

Special Populations

Geriatrics (≥ 65 years)

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

Renal Impairment

There is a close relationship between renal function and clearance of miglustat. Exposure of miglustat is markedly increased in patients with severe renal impairment.

In patients with mild renal impairment (adjusted creatinine clearance 0.83-1.2 mL/s or 50-70 mL/min /1.73 m^2) Sandoz Miglustat administration should commence at a dose of 100 mg twice per day in patients with Type 1 Gaucher disease and at a maximum dose of 200 mg twice per day with Niemann-Pick Type C disease. Starting dose should be adjusted for body surface area in pediatric patients (4-12 years of age) with Niemann-Pick Type C disease.

In patients with moderate renal impairment (adjusted creatinine clearance of 0.5-0.83 mL/s or 30-50 mL/min/1.73 m^2), Sandoz Miglustat administration should commence at a maximum dose of 100 mg once per day in patients with Type 1 Gaucher disease and at a dose of 100 mg twice per day with Niemann-Pick Type C disease. Starting dose should be adjusted for body surface area in pediatric patients (4-12 years of age) with Niemann-Pick Type C disease.

Use in patients with severe renal impairment (creatinine clearance of < 0.5 mL/sec or 30 mL/min/1.73 m^2) is not recommended. In patients with renal impairment continued monitoring and appropriate dosage adjustment is recommended.

Hepatic Impairment

Miglustat has not been evaluated in patients with moderate to severe hepatic impairment. No metabolites of miglustat have been detected in animals or in humans either in-vivo or in-vitro. Miglustat is known to be substantially excreted by the kidney. There is insufficient clinical experience in patients with hepatic impairment to provide dosing recommendations.

4.3 Reconstitution

No reconstitution required.

4.4 Administration

Capsules should be swallowed whole with water.
Sandoz Miglustat can be taken with or without food. The risk of diarrhea may be reduced if Sandoz Miglustat is taken between meals (see 7 WARNINGS AND PRECAUTIONS).

4.5 Missed Dose

If a scheduled dose of Sandoz Miglustat is missed, a double dose should not be taken to make up for the forgotten individual dose. The patient should take the next dose at the usual scheduled time.

5 OVERDOSAGE

In the clinical development program for miglustat, no patient experienced an overdose of study drug. However, miglustat has been administered at doses of up to 3000 mg/day (approximately 10 times the recommended dose administered to Gaucher patients) for up to six months in Human Immunodeficiency Virus (HIV)-positive patients. Adverse events observed in the HIV studies included granulocytopenia, dizziness, and paresthesia. Leukopenia and neutropenia have also been observed in a similar group of patients receiving 800 mg/day or above.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Capsule / 100 mg	Capsule contents: magnesium stearate, povidone, and sodium starch glycolate. Capsule shell: gelatin and titanium dioxide

Sandoz Miglustat capsules are supplied in hard capsules containing 100 mg of miglustat. Sandoz Miglustat 100 mg are white opaque capsules filled with white to off white granulate.

Sandoz Miglustat capsules are supplied in boxes containing 5 blister cards of 18 capsules each (90 capsules/box).

7 WARNINGS AND PRECAUTIONS

Therapy should be directed by physicians knowledgeable in the management of patients with Gaucher disease or Niemann-Pick Type C disease, as appropriate.

General

Severe Gaucher Disease: The safety and efficacy of miglustat have not been specifically evaluated in patients with severe Gaucher disease, defined as hemoglobin concentration below 9 g/dl or a platelet count below 50 x 10^9/L or active bone disease.

Carcinogenesis and Mutagenesis

Evidence of carcinogenicity and mutagenicity with miglustat is limited to non-clinical findings (see 16 NON-CLINICAL TOXICOLOGY).

Dependence/Tolerance

The dependence potential of miglustat has not been evaluated in human studies.

Driving and Operating Machinery

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

Gastrointestinal

Gastrointestinal events, mainly diarrhea, have been observed in more than 85% of patients, either at the outset of treatment or intermittently during treatment. The mechanism is probably inhibition of intestinal disaccharidases such as sucrose-isomaltase in the gastrointestinal tract leading to reduced absorption of dietary disaccharides in the small intestine. The majority of cases are mild and are expected to resolve spontaneously on therapy. In clinical practice, miglustat-induced gastrointestinal events have been observed to respond to individualized diet modification (reduction of sucrose, lactose and other carbohydrate intake), to taking miglustat between meals, and/or to anti-diarrheal medication such as loperamide. In some patients, temporary dose reduction may be necessary. Discontinuation may be necessary if symptoms persist or become severe. Patients with chronic diarrhea or other persistent gastrointestinal events that do not respond to these interventions should be investigated according to clinical practice. Miglustat has not been evaluated in patients with a history of significant gastrointestinal disease, including inflammatory bowel disease.

Hematologic

Reductions in hemoglobin and platelet count without association with bleeding were observed in patients with Type 1 Gaucher disease who were switched from enzyme replacement therapy to miglustat (see 8.4 Abnormal Laboratory Findings). In line with standard clinical practice in Type 1 Gaucher disease, monitoring of platelet counts is recommended in all patients.

Reductions in platelet counts without association to bleeding were observed in some patients with Niemann-Pick Type C disease treated with miglustat. Monitoring of platelet counts is recommended in these patients.

Monitoring and Laboratory Tests

All patients should undergo baseline and repeat neurological evaluation.

Patients with Type 1 Gaucher disease should have their disease status regularly monitored by assessment of spleen and liver volumes and hematologic analysis. Monitoring of platelet counts is recommended in patients with Type 1 Gaucher disease. Monitoring of vitamin B12 level is recommended because of the high prevalence of vitamin B12 deficiency in patients with Type 1 Gaucher disease.

The benefit of treatment with Sandoz Miglustat for neurological manifestations in patients with Niemann-Pick Type C disease should be evaluated on a regular basis, e.g., every 6 months.

Monitoring of platelet counts and renal function is recommended in patients treated for Niemann-Pick Type C disease with Sandoz Miglustat (see 7 WARNINGS AND PRECAUTIONS, **Hematologic** and **Renal**).

Miglustat has not been evaluated in patients with a history of or in the presence of cataracts. Regular follow-up is recommended in these patients (see 16 NON-CLINICAL TOXICOLOGY).

Neurologic

Cases of peripheral neuropathy and tremor have been reported in patients treated with miglustat 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 (See 8.2 Clinical Trial Adverse Reactions, **Neurological**).

All patients should undergo baseline and repeat neurological evaluation. Patients who develop symptoms such as numbness and tingling should have a careful re-assessment of risk-benefit.

Renal

Sandoz Miglustat should be used with caution in patients with renal impairment.
Miglustat is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. The clearance of miglustat is decreased by 40 to 60% in patients with mild to moderate renal impairment, and up to 70% in patients with severe renal impairment. As a result of this, dose reductions are recommended for those patients with mild to moderate renal impairment, the reduction being dependent upon the level of their creatinine clearance adjustment (see 4.2 Recommended Dose and Dosage Adjustment). For those patients with severe renal impairment, treatment with miglustat is not recommended. Since elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Reproductive Health: Female and Male Potential

- **Fertility**

Males: Reliable contraceptive methods should be maintained while male patients are taking Sandoz Miglustat and for 3 months following discontinuation. Male patients should be informed that it may affect the semen. Female partners of male patients treated with Sandoz Miglustat should also consider reliable contraception.

Studies in rats have shown that miglustat adversely affects spermatogenesis, sperm parameters and reduces fertility. These effects were seen at doses that gave similar exposure as the proposed human therapeutic dose.

Females: No data are available on female fertility in humans following the use of miglustat. Animal studies demonstrated elevations in post-implantation losses and increases in embryonic death with miglustat administration.

- **Teratogenic Risk**

Patients should be informed of the potential hazard to the foetus.
Sandoz Miglustat is contraindicated in women who are or may become pregnant. All females should have a pregnancy test before using Sandoz Miglustat. Women of childbearing potential taking Sandoz Miglustat should use a reliable method of contraception. See 2 CONTRAINDICATIONS.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies of miglustat in pregnant women. Studies in animals have shown maternal and embryo-fetal toxicity, including decreased embryo-fetal survival, and prolonged and difficult parturition. The potential risk for humans is unknown. Miglustat crosses the placenta and should not be used during pregnancy. Contraceptive measures should be used by women of child-bearing potential. See 2 CONTRAINDICATIONS and 16 NON-CLINICAL TOXICOLOGY.

7.1.2 Breast-feeding

It is not known if miglustat is secreted in breast milk. Sandoz Miglustat should not be used in nursing mothers.

7.1.3 Pediatrics

There is no experience with the use of miglustat in patients with Type 1 Gaucher disease under the age of 18. Patients below 4 years of age were not enrolled in the prospective study of miglustat in Niemann-Pick Type C disease. See 4 DOSAGE AND ADMINISTRATION.

Reduced growth has been reported in some pediatric 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 pediatric and juvenile patients during treatment with Sandoz Miglustat; the benefit/risk balance should be re-assessed on an individual basis for continuation of therapy.

7.1.4 Geriatrics (≥ 65 years)

Clinical studies of miglustat did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Type 1 Gaucher Disease

The safety of miglustat in patients with Type 1 Gaucher disease has been assessed in the core and extension periods of six open-label monotherapy studies where 132 patients were exposed to miglustat. Most of the 132 patients with Type 1 Gaucher disease in the combined data set from the clinical studies reported at least one adverse event during their treatment period. These events appeared at the outset of treatment or occurred intermittently during treatment. The most frequent (≥ 10%) adverse reactions were diarrhea (83%), weight decrease (49%), flatulence (52%), abdominal pain (23%), abdominal pain upper (14%), tremor (29%), headache (14%), fatigue (10%) and nausea (10%). The majority of cases were mild or moderate in severity, and resolved spontaneously, after dose reduction, or upon treatment discontinuation. See 7 WARNINGS AND PRECAUTIONS.

Forty-three (32.6%) of the 132 patients exposed to miglustat for at least 5 years withdrew from the study due to an adverse event. The most frequent adverse events leading to withdrawal were associated with gastrointestinal symptoms (diarrhea; 12.9%, flatulence; 4.5%, abdominal pain; 1.5%) or neurological symptoms (tremor; 4.5%, paraesthesia; 2.3%, hypoaesthesia; 1.5%). With regards to all patients enrolled during the first 6 months of treatment, withdrawals due to adverse events were more common in the 100 mg three times a day miglustat treatment group (11%) than in the 50 mg three times a day miglustat (6%) or the Combination treatment groups (3%).

Twenty-three (29%) patients had an adverse event that resulted in a dose reduction. The most common of these adverse events were diarrhea, weight loss, and tremor. During the first 6 months of treatment, dose reductions due to adverse events were more common in the combination treatment group than in the 100 mg three times a day miglustat (6%) and 50 mg three times a day miglustat (4%) treatment groups.

Niemann-Pick Type C Disease

The safety information of miglustat in Niemann-Pick Type C disease has been assessed in a prospective open-label clinical trial and an uncontrolled sub-study where 40 patients were exposed to miglustat. Of the 40 Niemann-Pick Type C patients, 97.5% experienced at least one adverse event during their treatment period. The most frequently occurring adverse events were diarrhea (82.5%), weight decrease (60.0%), tremor (57.5%), and flatulence (55%).

Nine patients withdrew from the study because of an adverse event including two from the pediatric (4-12 years of age) population.

Serious Adverse Drug Reactions

Three non-fatal serious adverse events reported by two patients in clinical studies were considered to be related to miglustat (neuritis and neuropathy; neuropathy) and these events occurred after 65 weeks of treatment (one event occurred 2.5 months after miglustat discontinuation).

In patients with Type 1 Gaucher disease, isolated additional serious adverse drug reactions were reported from ongoing studies and include the following: gastrointestinal polyposis, and cerebellar syndrome**.**

In patients with Niemann-Pick Type C disease, 11 patients reported a total of 23 serious adverse events. The most frequent serious adverse events were infections and infestations and gastrointestinal disorders. None of the serious adverse events leading to discontinuation was considered related to miglustat treatment.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Type 1 Gaucher Disease
Information presented in this section represents findings of 132 patients miglustat-treated patients from the core (0-12 months) and extension (12-54 months) periods of six clinical studies OGT 918-001, OGT 918-003, OGT 918-004, OGT 918-005, OGT 918-011 and OGT 918-016. A total of 132 patients were treated with miglustat and were included in the safety population. This included 28 patients from study OGT 918-001 (100 mg three times a day), 18 patients from study OGT 918-003 (50-100 mg three times a day), 34 patients from study OGT 918-004 (100 mg three times a day), 10 patients from study OGT 918-005 (100 mg three times a day) and 42 patients from study OGT 918-011 (100 mg three times a day). The mean exposure was 2.1 years with 81% of the patients exposed for at least 6 months and 37% exposed for at least 2 years. Study OGT 918-011 was an open-label, non comparative 2-year study of 42 patients with Type 1 Gaucher disease who received a minimum of 3 years enzyme replacement therapy and who fulfilled criteria of stable disease for at least 2 years. Study OGT 918-016 included patients previously enrolled in studies OGT 918-001, -003, and -004.

Adverse reactions by MedDRA Primary System Organ Class and Preferred Term with an incidence of >1% of patients treated with miglustat are presented below in Table 1.

Table 1 - Adverse Reactions by Primary System Organ Class and Preferred Term Occurring in Type 1 Gaucher Disease patients with an Incidence of >1%

ADVERSE REACTIONS	Miglustat (N=132)	
Primary System Organ Class: Preferred Term	**N**	**%**
Blood and Lymphatic System Disorders		
Thrombocytopenia	6	5
Ear and Labyrinth Disorders		
Vertigo	2	2
Eye Disorders		
Vision Blurred	2	2
Gastrointestinal Disorders		
Diarrhea	110	83
Flatulence	68	52
Abdominal Pain	30	23
Abdominal Pain Upper	19	14
Nausea	13	10
Abdominal Distension	10	8
Abdominal Discomfort	8	6
Constipation	7	5
Vomiting	3	2
Dyspepsia	5	4
Gastrointestinal Pain	4	3
Dry mouth	2	2
Gastritis	2	2
General Disorders and Administration Site Conditions		
Fatigue	13	10
Asthenia	7	5
Chills	2	2
Malaise	2	2
Chest Pain	2	2
Feeling Jittery	2	2
Investigations		
Weight Decreased	64	49
Metabolism and Nutrition Disorders		
Decreased Appetite	11	8
Musculoskeletal and Connective Tissue Disorders		
Muscle Spasms	12	9
Muscular Weakness	3	2
Arthralgia	2	2
Bone Pain	2	2
Nervous Systems Disorders		
Tremor	38	29

ADVERSE REACTIONS	Miglustat (N=132)	
Primary System Organ Class: Preferred Term	**N**	**%**
Headache	18	14
Dizziness	11	8
Paresthesia	11	8
Hypoesthesia	7	5
Neuropathy Peripheral	4	3
Amnesia	3	2
Coordination Abnormal	2	2
Disturbance in Attention	2	2
Memory Impairment	2	2
Migraine	2	2
Psychiatric Disorders		
Insomnia	3	2

Niemann-Pick Type C Disease

The safety information of miglustat in Niemann-Pick Type C disease presented in this section comes from a prospective open-label clinical trial. The clinical trial included 29 adult and juvenile patients in a 12-month controlled period, followed by extension therapy for an average total duration of 3.9 years and up to 5.6 years. In addition, 12 pediatric patients (4 to 12 years of age) were enrolled in an uncontrolled sub study for an overall average duration of 3.1 years and up to 4.4 years. Among the 40 patients exposed to miglustat in the trial 14 patients were treated for more than 3 years.

In patients included in the clinical trial, 40%-50% had platelet counts below the lower limit of normal at baseline.

Adverse events by with an incidence of >1 patient treated with miglustat are presented below in Table 2 and Table 3.

Table 2 – Adverse Events Occurring in Niemann-Pick Type C juvenile and adult patients with an incidence of >1 patient treated with miglustat

	Miglustat (N=20)[1]		No Treatment (N=9)[1]	
	N	(%)	N	(%)
Gastrointestinal system				
Diarrhea	17	85	4	44
Flatulence	14	70	0	0
Abdominal pain	9	45	0	0
Nausea	7	35	1	11

	Miglustat (N=20)[1]		No Treatment (N=9)[1]	
	N	(%)	N	(%)
Vomiting	6	30	0	0
Abdominal distension	4	20	0	0
Abdominal discomfort	3	15	0	0
Central and peripheral nervous systems				
Tremor	11	55	2	22
Headache	9	45	3	33
Gait spastic	5	25	1	11
Paresthesia	4	20	1	11
Dysphagia	4	20	4	44
Intention tremor	3	15	0	0
Dystonia	3	15	2	22
Sensory loss	2	10	1	11
Gait abnormal	2	10	4	44
Dysarthria	2	10	1	11
Clonic convulsion	2	10	0	0
Ataxia	2	10	1	11
Investigations				
Weight decreased	13	65	0	0
Infections and infestations				
Nasopharyngitis	7	35	3	33
Psychiatric disorders				
Depression	4	20	0	0
Insomnia	6	30	0	0
Agitation	3	15	0	0
Sleep disorder	2	10	0	0
General disorders and administration site conditions	7	35	1	11
Fatigue				
Peripheral coldness	2	10	0	0
Fall	2	10	2	22
Influenza like illness	2	10	0	0

	Miglustat (N=20)[1]		No Treatment (N=9)[1]	
	N	(%)	N	(%)
Injury, poisoning and procedural complications	3	15	1	11
Laceration				
Contusion	3	15	0	0
Metabolism and nutrition disorders				
Appetite decreased	5	25	0	0
Musculoskeletal disorders				
Pain in limb	2	10	2	22
Arthralgia	3	15	0	0
Muscle cramps	2	10	0	0

1. Patients include those from the primary (0-12 months) phase of Study OGT 918-007 in juvenile and adult patients.

Table 3 – Adverse Events Occurring in Niemann-Pick Type C pediatric patients (4 to 12 years of age) with an incidence of >1 patient treated with miglustat

	Miglustat (N=12) [1]	
	N	(%)
Gastrointestinal system		
Diarrhea	8	67
Vomiting	4	33
Flatulence	4	33
Abdominal pain	2	17
Central and peripheral nervous systems		
Gait abnormal	4	33
Hyperreflexia	3	25
Dysphagia	3	25
Ataxia	3	25
Tremor aggravated	2	17
Tremor	2	17
Supranuclear palsy	2	17
Gait spastic	2	17

	Miglustat (N=12) [1]	
	N	(%)
Dystonia	2	17
Headache	2	17
Saccadic eye movement	2	17
Investigations		
Weight decreased	3	25
Infections and infestations		
Nasopharyngitis	4	33
Sinusitis	3	25
Respiratory tract infection	2	17
Gastroenteritis viral	2	17
Ear infection	2	17
General disorders and administration site conditions	5	42
Fatigue		
Lethargy	2	17
Fall	2	17
Dehydration	2	17
Respiratory, thoracic and mediastinal disorders	4	33
Cough		
Epistaxis	2	17
Injury, poisoning and procedural complications	2	17
Laceration		

1. Patients include those from the primary (0-12 months) phase of Study OGT 918-007 in

pediatric patients.

Gastrointestinal

Diarrhea: Diarrhea has been reported in approximately 85% of patients treated with miglustat in clinical trials in Type 1 Gaucher Disease and Niemann-Pick Type C disease. See 7 WARNINGS AND PRECAUTIONS.

Weight Loss: Weight loss has been observed in approximately 52% of Type 1 Gaucher and 60 % of Niemann-Pick Type C patients treated with miglustat. The greatest effect was at 12 months, with a mean weight loss of 6 – 7% of body weight.

Neurological

Approximately 37% of patients in clinical trials in Type 1 Gaucher and 58% of Niemann-Pick Type C disease patients reported tremor on treatment. In Type 1 Gaucher disease, tremors were described as an exaggerated physiological tremor of the hands. Tremor usually began within the first month of treatment with miglustat, 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.

Cases of peripheral neuropathy have been reported in patients treated with miglustat with or without concurrent conditions such as vitamin B12 deficiency and monoclonal gammopathy.

8.3 Less Common Clinical Trial Adverse Reactions

The following adverse drug reactions were reported from clinical trials in patients with Type 1 Gaucher disease with an incidence of ≤1%.

Blood and lymphatic system disorders: leucopenia.
Cardiac disorders: supraventricular extrasystoles.
Congenital, familial and genetic disorders: Gaucher's disease.
Ear and labyrinth disorders: tinnitus.
Eye disorders: blepharospasm.
Gastrointestinal disorders: abnormal feces, epigastric discomfort, eructation, gastric polyps, intestinal polyp, irritable bowel syndrome, paresthesia oral.
General disorders and administration site conditions: influenza like illness, pain, pyrexia.
Infections and infestations: nasopharyngitis, urinary tract infection.
Investigations: aspartate aminotransferase increased, blood folate decreased, cell marker increased, electrophoresis protein abnormal, hepatic enzyme increased, mean cell volume decreased, monoclonal immunoglobulin present, platelet morphology abnormal, vitamin B1 decreased, weight increased.

Metabolism and nutrition disorders: lactose intolerance.
Musculoskeletal and connective tissue disorders: back pain, myalgia, pain in extremity.
Nervous system disorder: axonal neuropathy, cerebellar syndrome, decreased vibratory sense, hyperreflexia, intention tremor, peripheral sensory neuropathy, sensory loss.
Psychiatric disorders: depression, emotional distress, loss of libido, premature ejaculation, sleep disorder.
Reproductive system and breast disorders: erectile dysfunction, hypomenorrhea, menstruation irregular.
Skin and subcutaneous tissue disorders: alopecia, ecchymosis, hyperhidrosis, hypoesthesia facial, increased tendency to bruise, pruritus.
Vascular disorders: flushing.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Type 1 Gaucher disease

Table 4: Parameters that changed by more than 10% between baseline and months indicated

Parameter	6 Months	12 Months	18 Months
eosinophils	+19.8%	21.7%	23.1%
basophils	+36.2%	N/A	-31.7%
Partial thromboplastin	+36.2%	N/A	N/A

It would be expected that hemoglobin, hematocrit, red blood count and platelets would increase over time as this is the intended treatment effect of the drug. These expected increases are seen from Month 24 onwards for these parameters:

Table 5: Parameters that changed by more than 10% between baseline and 24 months onwards

Parameter	24 Months	30 Months	36 Months
RBC	N/A	+10.5%	N/A
Platelets	+25.7%	+29.1%	+33.1
Hematocrit	+10.8%	+13.0%	+12.4%
lymphocytes	+14.2%	+21.1%	N/A
Monocytes	+10.8%	+15.7%	N/A
Basophils	-27.6%	-51.9%	-39.8%

Table 6: Clinical trial OGT 918-011, observation between baseline and after completion of 24 months of miglustat treatment in 21 patients

	Mean reduction	95% CI

hemoglobin	-0.95 g/dL	-1.38, -0.53
Platelet count	-44.1 × 10^9/L	–57.6, –30.7

Analyses of clinical chemistry abnormalities from five clinical trials in patients with Type 1 Gaucher disease (Studies OGT 918-001, OGT 918-003, OGT 918-004, OGT 918-005, and OGT 918-016), revealed marked increases in ALT and AST for 3.4% and 5.0% of patients, respectively. One patient also had a marked increase in alkaline phosphatase. A summary of these clinical chemistry abnormalities is provided in Table 7. Marked laboratory abnormalities were calculated using a combination of the Marked Reference Range and clinically relevant change from baseline (% increase or % decrease or both, depending on the laboratory test).

Table 7 - Incidence of marked clinical chemistry abnormalities up to 28 days after the end-of-study treatment in the miglustat-treated Type-1 Gaucher disease patients.

Parameter	**Standard Reference Range**	**Marked Reference Range (Relevant change from baseline)[1]**	**Miglustat-treated Type-1 Gaucher disease patients [a] N=132**	
			n / n'	**(%)**
ALT	0-30 U/L	0-60 U/L (> +50%)	3/87	(3.4)
AST	0-25 U/L	0-50 U/L (> +50%)	4/80	(5.0)
Alkaline Phosphatase	0-100 U/L	0-190 U/L (> +50%)	1/87	(1.1)
Sodium	133-145 mmol/L	130-150 mmol/L (< -7%)	1/87	(1.1)

n'= number of patients with at least one post-baseline measurement for the related parameter
a = in Study OGT 918-011, clinical chemistry evaluation only comprised vitamins B1 and B12, hence the low n'
ALT = alanine aminotransferase, AST = aspartate aminotransferase,
1. Sponsor's marked reference range and relevant % change from baseline

Niemann-Pick Type C disease

The median of platelet counts at treatment start was around 160 × 10^9/L and slightly decreased below 150 × 10^9/L during the first year of treatment. After that, the median platelet count remained stable above 130 × 10^9/L. Of note, 39% of the patients already had platelet counts below the lower limit of normal at screening. Reduced platelet count is a common finding in Niemann-Pick Type C disease.

8.5 Post-Market Adverse Reactions

The reporting rates for the most commonly reported events were 18.5% for diarrhea, 12.3% for weight decrease, 8.6% for tremor, 4.4% for unspecified neurological symptoms, 3.3% for memory impairment, and 2.6% for convulsions.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Miglustat does not inhibit the metabolism of various substrates of cytochrome P450 enzymes and miglustat is not metabolised by these enzymes. Consequently, significant interactions are unlikely with drugs that are substrates/inducers/inhibitors of cytochrome P450 enzymes. No significant drug interactions have been observed with miglustat that would affect the dosing recommendations for miglustat.

9.4 Drug-Drug Interactions

Imiglucerase:
Drug interaction between miglustat (100 mg orally three times daily) and imiglucerase (7.5 or 15 U/kg/day) was assessed in imiglucerase stabilized Type 1 Gaucher patients after one month of co-administration. There was no significant effect of imiglucerase on the pharmacokinetics of miglustat, with the co-administration of imiglucerase and miglustat resulting in a 22% reduction in C_{max} and a 14% reduction in AUC of miglustat. Limited data indicate that miglustat has no or little effects on the pharmacokinetics of imiglucerase .

Loperamide:
A population pharmacokinetic analysis indicated that concomitant loperamide administration during clinical trials did not alter the pharmacokinetics of miglustat.

There is no change in the dosing recommendations when miglustat is co-administered with imiglucerase and/or loperamide.

The potential for metabolism of miglustat was evaluated in an in vitro study in human, rat, and primate liver microsomes. No metabolism of miglustat was evident in any of the in vitro incubation supernatants analysed, indicating that miglustat is not appreciably metabolized by cytochrome P450 in humans, rats, or primates.

Miglustat does not inhibit the metabolism of various substrates of cytochrome P450 enzymes; consequently, significant interactions are unlikely with drugs that are substrates of cytochrome P450 enzymes.

9.5 Drug-Food Interactions

Co-administration of miglustat with food results in a decrease in the rate of absorption of miglustat but has no statistically significant effect on the extent of absorption of miglustat.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Miglustat functions as a competitive and reversible inhibitor of the enzyme glucosylceramide synthase, the initial enzyme in a series of reactions which results in the synthesis of most glycosphingolipids. Miglustat helps to reduce the rate of glycosphingolipid biosynthesis so that the amount of glycosphingolipid substrate is reduced to a level which allows the residual activity of the deficient glucocerebrosidase enzyme to be more effective (substrate reduction therapy). Miglustat crosses the blood-brain barrier.

10.2 Pharmacodynamics

Miglustat inhibits glucosylceramide synthase, thus reducing the rate of glycosphingolipid biosynthesis such that the amount of substrate the defective enzyme has to catabolize is reduced to a level which matches the residual glucocerebrosidase activity. This approach termed Substrate Reduction Therapy allows a balance between glycosphingolipid synthesis and degradation, thereby reducing storage and its associated pathology.

10.3 Pharmacokinetics

Miglustat exhibits linear, dose-proportional pharmacokinetics over a wide dose range (approximately 50-1120 mg single doses).

Based on a cross-study population pharmacokinetic analysis using data from Gaucher and Fabry patients, no significant effects were found with any of the demographic covariates tested in this analysis: no effect of age (range 18 to 69 years), body mass index (range of 16.9 to 33.1 kg/m^2), or gender was found on the pharmacokinetics of miglustat.

Based on a cross-study population pharmacokinetic analysis using data from Gaucher and Fabry

patients, several efficacy measurements (liver response, spleen response, platelet response, and hemoglobin response, measured at six months) were evaluated for correlation with miglustat pharmacokinetics, of which only spleen response showed a significant relationship with steady-state concentrations. Patients with higher miglustat steady-state concentrations are more likely to experience a favourable spleen response (decrease in spleen volume) than those with lower concentrations. Of the adverse events (diarrhea and tremor) examined in this analysis, only diarrhea showed concentration dependence, with patients with higher steady-state concentrations being more likely to experience a greater intensity of diarrhea than patients with low concentrations. See 4 DOSAGE AND ADMINISTRATION.

Table 8 - Summary of Miglustat's Pharmacokinetic Parameters in Patients with Type 1 Gaucher disease and Niemann-Pick Type C disease

	C_{max}	$t_{1/2}$	AUC_{0-6hr}	Clearance	Volume of distribution
Adult patients with Type 1 Gaucher disease **Single dose (100 mg)**	862 ng/mL	7.3 hr	3746 ng·hr/mL	11.8-13.8 L/hr	83-105 L
Adult patients with Type 1 Gaucher disease **Month 1 (100mg, 3 times daily)**	1922 ng/mL	6.4 hr	8911 ng·hr/mL	-	-
Juvenile/adult patients (over 12 years) with Niemann-Pick Type C disease **Month 1 (200 mg, 3 times daily)**	2698 ng/mL	3.0 hr (tmax)	16412[a]	-	-
Pediatric patients (4-12 years) with Niemann-Pick Type C disease					
Month 1 (200 mg, 3 times daily)	2075 ng/mL	4.0 hr (tmax)	11975[a]	-	-
Month 1 (200 mg, 2 times daily)	3289 ng/mL	3.54 hr (tmax)	18792[a]	-	-
Month 1 (200 mg, once daily)	2223 ng/mL	4.0 hr (tmax)	15866[a]	-	-

[a]$AUC_{0\text{-}8hr}$

Absorption:
In healthy subjects miglustat is rapidly absorbed following oral administration, with a t_{max} of approximately 2 to 2.5 hours. Co-administration of miglustat with food results in a decrease in the rate of absorption of miglustat (C_{max} was decreased by 36% and t_{max} delayed 2 hours) but has no statistically significant effect on the extent of absorption of miglustat (AUC decreased by 14%). Miglustat's pharmacokinetics remain stable after repeated dosing three times daily for up to 12 months.

The pharmacokinetics of miglustat is similar in adult Type 1 Gaucher disease patients and Niemann-Pick Type C disease patients when compared to healthy subjects. Pharmacokinetic data were obtained in pediatric patients with Type 3 Gaucher disease aged 3–15 years and patients with Niemann-Pick Type C disease aged 5–16 years. Dosing in children at 200 mg three times a day adjusted for body surface area resulted in C_{max} and AUCτ values which were approximately two-fold those attained after 100 mg three times a day 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. No significant relationships or trends were noted between miglustat pharmacokinetic parameters and demographic variables (age, gender, and body mass index).

The pharmacokinetics of miglustat were evaluated in patients with Type 1 Gaucher disease who received 100 mg miglustat three times daily for a period of 12 months. Five patients had serial blood samples collected at pre-dose and at various times up to 24 hours following dosing on Day 1 and at Month 1 in order to evaluate the pharmacokinetic profile of miglustat after single and multiple dosing. Mean miglustat pharmacokinetic parameters for these five patients are as follows:

Table 9 - Mean Miglustat Pharmacokinetic Parameters

Sampling Time	C_{max} (ng/ml)	t_{max} (hr)	$AUC_{0\text{-}6h}$ (ng·hr/mL)	$AUC_{0\text{-}4}$ (ng·hr/mL)	$t_{½}$	R_{lin}	R_O
Day 1	862 (16)	2.5 (2-4)	3746 (23)	9502 (22)	7.30 (17)	NA	NA
Month 1	1922 (9)	2.0 (1-2.5)	8911 (22)	NA	6.39 (22)	0.889 (7)	2.25 (18)

Values are mean with coefficient of variation in parentheses: n = 5 patients: NA = Not applicable
t_{max} values are median with range of values in parentheses
The dosing interval, τ, was 6 hours
R_{lin} = Linearity ratio (comparison of $AUC_{0\text{-}4}$ to $AUC_{0\text{-}\tau}$)

R_O = Observed degree of accumulation of miglustat in plasma at Month 1 (comparison of $AUC_{0-\tau}$ at Month 1 to $AUC_{0-\tau}$ on Day 1)

Following single and repeated oral doses of miglustat at 100 mg TID to these five patients, maximum plasma miglustat concentrations were attained, on average, at 2.0 to 2.5 hours post-dose. Thereafter, plasma miglustat concentrations declined with a mean apparent terminal half-life of approximately 6 to 7 hours. Based on this estimate, steady-state concentrations are expected to be achieved by 1.5 to 2 days following start of treatment.

Peak and trough plasma concentrations of miglustat were approximately 1400 to 1600 ng/mL, and 800 to 1000 ng/mL, respectively throughout the 12-month study duration. Steady-state concentrations were thus attained by at least Day 15 and were maintained up to 12 months of repeated oral dosing.

Eighteen patients continued into an extended 12-month treatment period. Patients received once daily doses of 100 mg miglustat or 100 mg miglustat every 16 hours versus three times daily doses in the initial treatment period. Mean peak and trough plasma concentrations after three-times daily dosing were approximately 1.3 and 1.9-fold greater, respectively, than those concentrations after once-daily dosing. Excessive accumulation of miglustat in plasma of patients with Gaucher disease is not expected, as indicated by the previously reported accumulation index and the estimated half-life of miglustat (2.3 and 6-7 hours, respectively).

Distribution:
Mean apparent volume of distribution of miglustat is 83-105 L in Type 1 Gaucher Disease patients, indicating that miglustat distributes into extravascular tissues. Miglustat does not bind to plasma proteins. However, tissue distribution studies in rats have shown no evidence of retention in any tissues. V/F is also affected by renal function, though the effect is not as clear as with CL/F. Results generally suggested an approximate 40% increase in V/F with increasing renal impairment.

The in-vitro plasma protein and red blood cell binding of [^{14}C]-miglustat was evaluated in rat, monkey and man. No binding to plasma proteins was observed in any of the three species analysed within the concentration range of 1.0 - 20.0 mcg/ml. The mean percentage of association with red blood cells of [^{14}C]-miglustat was moderate (36.0%, 39.2%, and 38.8% in rat, monkey and human blood, respectively. There was no evidence of concentration dependent binding to red blood cells. The mean level of association of miglustat in each species correlated well with the mean packed cell volume (hematocrit) for each species, suggesting that the level of association can be explained by free partitioning of [^{14}C]-miglustat across the cell membrane.

No binding to the cell surface or specific accumulation of miglustat within blood cells was observed. The mean blood: plasma ratios for [^{14}C]-miglustat in rat, monkey and human blood were 0.943, 0.941, and 0.877, respectively.

Metabolism:
No metabolites of miglustat were detected *in vitro* or *in vivo*. Miglustat is excreted unchanged in urine.

Elimination:
The major route of excretion of miglustat is renal. Renal impairment has a significant effect on the pharmacokinetics of miglustat, resulting in increased systemic exposure to miglustat in such patients.

The results of a cross-study population pharmacokinetics analysis from Gaucher and Fabry patients have shown that miglustat is a low clearance drug (mean apparent oral clearance (CL/F) of 11.8-13.8 L/hr in Gaucher patients).

A mass balance study was conducted in 6 HIV-1 positive patients, using a perbutyrated prodrug (OGT 924) of miglustat. Total radioactivity in plasma after a 125 mg dose peaked at approximately 3.5 hours (median value) and was no longer detectable by 48-72 hours. The profile of total radioactivity in red blood cells paralleled that of plasma, though concentrations were lower. Miglustat accounted for the majority (mean 75%; range 57-85%) of the radioactivity measured in plasma and no detectable OGT 924 was found. Additionally, the profile and plasma concentrations of miglustat closely matched those of total radioactivity in plasma and red blood cells.

Ninety percent of the dose, on average (range 79-97%) was accounted for in the urine and feces. Of this, an average of 47% (range 42-59%) of the administered dose was excreted in urine, of which approximately 69% was excreted as miglustat. An average of 43% (range 32-52%) of the administered dose was excreted in feces.

Special Populations and Conditions

- **Geriatrics:** The pharmacokinetics of miglustat have not been evaluated in patients over the age of 65 years.

- **Sex:** No significant relationship or trend was noted between miglustat pharmacokinetic parameters and sex.

- **Ethnic Origin:** Ethnic differences in miglustat pharmacokinetics have not been evaluated in Type I Gaucher disease patients. Based on a cross analysis study, the apparent oral

clearance of miglustat in patients of Ashkenazi Jewish descent was not statistically different to that in others (1 Asian and 15 Caucasians).

- **Hepatic Insufficiency:** Miglustat has not been evaluated in patients with moderate to severe hepatic impairment. See 4 DOSAGE AND ADMINISTRATION. Miglustat pharmacokinetics are not affected by hepatic function under conditions of mild hepatic impairment.

- **Renal Insufficiency:** Pharmacokinetic data indicate increased systemic exposure to miglustat in patients with renal impairment. Limited data in patients with Fabry disease and impaired renal function indicate that oral clearance (CL/F) decreases with decreasing renal function. While the numbers of patients with mild to moderate renal impairment were small, the data suggest an approximate decrease in CL/F of 40% and 60%, respectively, in mild and moderate renal impairment, justifying the need to decrease the dose of miglustat in such patients. Based on a cross-study population pharmacokinetic analysis using data from Gaucher and Fabry patients, CL/F is significantly decreased with renal impairment, and correlates with the level of creatinine clearance (CLcr). At moderate and severe levels of renal impairment (CLcr <50 mL/min/1.73 m^2), CL/F is decreased by 60% to 70%. See 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION.

  Data in severe renal impairment are limited to two patients with creatinine clearance in the range 0.3-0.48 mL/s (18-29 mL/min). These data suggest a decrease in CL/F up to 70% in patients with severe renal impairment. Treatment with miglustat in patients with severe renal impairment is therefore not recommended. See 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION.

11 STORAGE, STABILITY AND DISPOSAL

Sandoz Miglustat should be stored at room temperature between 15 to 30°C. Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling requirements for Sandoz Miglustat.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

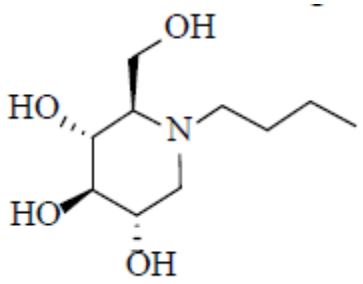
Drug Substance

Proper name: miglustat

Chemical name: 1,5-(butylimino)-1,5-dideoxy-D-glucitol

Molecular formula and molecular mass: $C_{10}H_{21}NO_4$ and 219.28 g/mol

Structural formula:



Physicochemical properties: White to off-white solid. Miglustat is readily soluble in water (>1000 mg/mL) and methanol. It is insoluble in *n*-heptane, dichloromethane and ethyl acetate.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Type 1 Gaucher Disease

Table 10 - Summary of patient demographics for clinical trials in Type 1 Gaucher Disease

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
OGT 918-001	Open-label, non-comparative	Starting dose: 100 mg three times a day oral. Dose adjustment allowed up to 300 mg three times a day based on plasma concentration, tolerability and organ volume response. Duration: 12 months	28	44.0 yrs (22-69)	14 M 14 F
OGT 918-001X (Extended phase)	Open-label, non-comparative	Dosing as above. Duration: 24 months (total 36 months).	18	43.2 yrs (22-62)	7 M 11 F
OGT 918-003	Open-label, non-comparative	Starting dose: 50 mg three times a day oral. Dose adjustment allowed down to 50 mg BID based on plasma concentration and/or tolerability. Duration: 6 months	18	42.4 yrs (22-61)	5 M 13 F
OGT 918-003X (Extended phase)	Open-label, non-comparative	As above. Dose could be decreased or increased (up to 300 mg three times a day) based on plasma concentration and/or tolerability. Duration: 6 months (total 12 months).	16	43.9 yrs (22-61)	4 M 12 F

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
OGT 918-004	Open-label, comparative	Starting dose for combination therapy or miglustat monotherapy : 100 mg three times a day oral miglustat. Could be reduced if patient experienced unacceptable side effects. Imiglucerase: patients received their existing dose. Duration: 6 months.	36	37.2 yrs (17-69)	16 M 20 F
OGT 918-004X (Extended phases)	Open-label, non-comparative	All patients were to continue taking miglustat at the dose they completed in the initial period (OGT 918-004) or were to receive 100 mg three times a day miglustat if commencing therapy for the first time i.e. switching from imiglucerase. Could be reduced if patient experienced unacceptable side effects. Duration: 12 months (total 18 months). 18 months (total 24 months)	 29 28	36.3 yrs (17-69)	14M 15F
OGT 918-005	Open-label, non-comparative	100 mg three times a day oral. Duration: 24 months	12	46.3 yrs (32-62)	9M 3F

The efficacy of miglustat in Type 1 Gaucher disease has been investigated in two non-comparative studies and one randomized comparative study with enzyme replacement given as imiglucerase (Table 10). Patients who received miglustat were treated with doses ranging from 100 mg a day to 600 mg a day, although the majority of patients were maintained on doses between 200 to 300 mg a day. The scheduled treatment periods were either six months or one year, and extension protocols were implemented in all three studies for patients to continue or

switch to treatment with miglustat. A total of 80 patients were exposed to miglustat during the three studies and their extension periods.

The primary efficacy end-points for the studies included liver and spleen organ volume response, biochemical and haematological response, and overall response. The secondary efficacy end-points included pharmacokinetic profiles, QoL questionnaire, and other disease assessments.

The safety and efficacy of miglustat have not been evaluated in patients with severe Type 1 Gaucher disease, defined as hemoglobin concentration below 9 g/dl or a platelet count below 50 x 10^9/L or active bone disease.

Open-Label Uncontrolled Monotherapy Studies

In study OGT 918-001, miglustat was administered at a starting dose of 100 mg three times daily for 12 months (dose range of 100 once-daily -200 mg three times daily) to 28 adult patients with Type 1 Gaucher disease, who were unable or unwilling to take enzyme replacement therapy, and who were treatment-naïve or had not taken enzyme replacement therapy in the preceding 6 months. Twenty-two patients completed the study. After 12 months of treatment, the results showed significant mean percent reductions from baseline in liver volume of 12% and spleen volume of 19% (see Table 11), a non-significant increase from baseline in mean absolute hemoglobin concentration of 0.26 g/dL (+2.6%) and a mean absolute increase from baseline in platelet counts of 8 x 10^9/L (+16.0%) (see Table 12).

In study OGT 918-003, miglustat was administered at a dose of 50 mg three times daily for 6 months to 18 adult patients with Type 1 Gaucher disease who were unable or unwilling to take enzyme replacement therapy and who were treatment-naïve or had not taken enzyme replacement therapy in the preceding 6 months. Seventeen patients completed the study. After 6 months of treatment, the results showed significant mean percent reductions from baseline in liver volume of 6% and spleen volume of 5% (see Table 11). There was a non-significant mean absolute decrease from baseline in hemoglobin concentration of 0.13 g/dL (-1.3%) and a non-significant mean absolute increase from baseline in platelet counts of 5 x 10^9/L (+2.0%) (see Table 12).

Extension Period

Eighteen patients were enrolled in a 12-month extension to study OGT 918-001. A subset of patients continuing in the extension had somewhat larger mean baseline liver volumes, and lower mean baseline platelet counts and hemoglobin concentrations than the original study population. After a total of 24 months of treatment, there were significant mean decreases from baseline in liver and spleen organ volume of 15% and 26%, respectively (see Table 11), and significant mean absolute increases from baseline in hemoglobin concentration and platelet counts of 0.9 g/L (+9.1%) and 14 x 10^9/L (+26.1%), respectively (see Table 12).

Sixteen patients were enrolled in a 6-month extension to study OGT 918-003. After a total of 12 months of treatment, there was a mean decrease from baseline in spleen organ volume of 10%, whereas the mean percent decrease in liver organ volume remained at 6% (see Table 11). There were no significant changes in hemoglobin concentrations or platelet counts (see Table 12).

Liver and spleen volume results from studies OGT 918-001 and OGT 918-003 are summarized in Table 11:

Table 11 - Liver and Spleen Volume Changes in 2 Open-Label Uncontrolled Monotherapy Studies of Miglustat with Extension Phases

Study	Liver Volume	Spleen Volume
	% Mean (N) (2-sided 95% CI)	% Mean (N) (2-sided 95% CI)
OGT 918-001 (dose miglustat 100 mg three times daily)		
Month 12, % Change from baseline	-12.1% (21) (-16.4, 7.9)	-19.0% (18) (-23.7, -14.3)
OGT 918-001 Extension Phase		
Month 24, % Change from baseline	-14.5% (12) (-19.3, 9.7)	-26.4% (10) (-30.4, -22.4)
OGT 918-003 (miglustat 50 mg three times daily)		
Month 6, % Change from baseline	-5.9% (17) (-9.9, -1.9)	-4.5% (11) (-8.2, -0.7)
OGT 918-003 Extension Phase		
Month 12, % Change from baseline	-6.2% (13) (-12.0, -0.5)	-10.1% (9) (-20.1, -0.1)

Hemoglobin concentration and platelet count results from studies OGT 918-001 and OGT 918-003 are summarized in Table 12:

Table 12 - Hemoglobin Concentration and Platelet Count Changes in 2 Open-Label Uncontrolled Monotherapy Studies of Miglustat with Extension Phases

Study	Hemoglobin Concentration	Platelet Count
	% Mean (N) (2-sided 95% CI)	% Mean (N) (2-sided 95% CI)
OGT 918-001 (dose miglustat 100 mg three times daily)		

Study	Hemoglobin Concentration	Platelet Count
	% Mean (N) (2-sided 95% CI)	% Mean (N) (2-sided 95% CI)
Month 12, % Change from baseline	+2.6% (22) (-0.5, 5.7)	+16.0% (22) (-0.8, 32.8)
OGT 918-001 Extension Phase		
Month 24, % Change from baseline	+9.1% (13) (2.9, 15.2)	+26.1% (13) (14.7, 37.5)
OGT 918-003 (miglustat 50 mg three times daily)		
Month 6, % Change from baseline	-1.3% (17) (-4.4, 1.8)	+2.0% (17) (-6.9, 10.8)
OGT 918-003 Extension Phase		
Month 12, % Change from baseline	+1.2% (13) (-5.2, 7.7)	+14.7% (13) (-1.4, 30.7)

A more pronounced improvement in hemoglobin concentration was seen at 18 and 24 months in patients with baseline (Month 0) hemoglobin concentrations <11.5 g/dL.

Open-Label Active-Controlled Study

Study OGT 918-004 was an open-label, randomized, active-controlled study of 36 adult patients with Type 1 Gaucher disease, who had been receiving enzyme replacement therapy with imiglucerase for a minimum of 2 years prior to study entry. Patients were randomized 1:1:1 to one of three treatment groups, as follows:

- Miglustat 100 mg three times daily alone
- Imiglucerase (patient's usual dose)
- Miglustat 100 mg three times daily + Imiglucerase (usual dose)

Patients were treated for 6 months, and 33 patients completed the 6-month study. At month 6, the results showed a significant decrease in mean percent change in liver volume in the combination treatment group compared to the imiglucerase alone group. There were no significant differences between the groups for mean absolute changes in liver volume. There were no significant differences between the groups for mean absolute and percent changes in spleen volume and hemoglobin concentration. However, there was a significant difference between the miglustat alone and imiglucerase alone groups in platelet counts at Month 6, with the miglustat alone group having a mean absolute decrease in platelet count of 21.6 x 10^9/L (-9.6%) and the imiglucerase alone group having a mean absolute increase in platelet count of 15.3 x 10^9/L (+10.1%) (see Table 13).

Table 13 - Changes of liver and spleen volume, hemoglobin concentration and platelet count in the three treatment arms (initial 6-month comparison phase)

	Imiglucerase alone		Miglustat alone		Combination	
Liver volume (n)	11		10		9	
Absolute change from baseline (Liters, mean (SD))	0.04	(0.16)	-0.05	(0.12)	-0.09	(0.12)
Percent change from baseline (%, mean, (SD))	3.5	(9)	-2.9	(7.9)	-4.9	(6.6)
Spleen volume (n)	8		7		7	
Absolute change from baseline (Liters, mean (SD))	-0.02	(0.06)	-0.27	(0.07)	-0.08	(0.13)
Percent change from baseline (%, mean, (SD))	-2.1	(4.8)	-4.8	(7.8)	-8.5	(17.7)
Hemoglobin concentration (n)	12		10		11	
Absolute change from baseline (g/dL, mean (SD))	-0.15	(0.39)	-0.31	(0.55)	-0.10	(0.72)
Percent change from baseline (%, mean, (SD))	-1.2	(3)	-2.4	(4.1)	-0.5	(6.2)
Platelet count (n)	12		10		11	
Absolute change from baseline (x 10^9/L, mean (SD))	15.3	(26.2)	-21.6	(37.4)	2.7	(34.4)
Percent change from baseline (%, mean, (SD))	10.1	(16.7)	-9.6	(15.1)	3.2	(18.6)

Extension Period

Twenty-nine patients were enrolled in a 6-month extension to study OGT 918-004. Twenty-eight of these 29 patients elected to enter a second extension phase and provide data for up to 24 months. In the extension phases, all patients had withdrawn from imiglucerase and received open-label miglustat 100 mg three times daily monotherapy.

Analysis of 24-month miglustat efficacy was conducted in 31 subjects who had received at least one dose of miglustat who had a baseline value and at least one post-baseline assessment for liver and spleen, hemoglobin or platelets. Baseline was defined as screening for subjects originally randomized to miglustat alone, and Month 6 for subjects originally randomized to imiglucerase alone or combination treatment who switched to miglustat alone after 6 months. Mean liver and spleen volume did not increase after switching from imiglucerase to miglustat monotherapy, with no statistically significant difference from baseline (see Table 14). Small decrease (<0.5 g/dL at the majority of time points) of mean hemoglobin concentration were observed after baseline, which were statistically significant at Months 6, 9, and 12 and 21 months' of miglustat treatment (see Table 15). No subject had a low hemoglobin that was

considered clinically significant at any time. A small statistically significant decrease of mean platelet count from baseline was observed upon switching from imiglucerase to miglustat monotherapy (see Table 15). Only one subject had low platelets reported as being clinically significant at any time and this subject already had low platelets at baseline.

Table 14 - Long-term organ volume changes up to 24 months of Miglustat treatment after Imiglucerase withdrawal

	Liver volume (Liters)		Spleen volume (Liters)	
Study OGT 918-004	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Baseline	29	1.78 (0.46)	20	0.66 (0.38)
6 months	29	1.78 (0.42)	21	0.86 (0.61)
% Change from baseline	27	-1.69 (10.27)	19	3.32 (16.31)
12 months[1]	8	1.58 (0.34)	6	0.52 (0.25)
% Change from baseline	8	-0.75 (6.44)	6	-6.13 (6.33)
18 months[2]	9	2.04 (0.43)	6	0.735 (0.41)
% Change from baseline	9	-3.89 (7.67)	6	-0.10 (9.69)
24 months[1]	5	1.47 (0.33)	4	0.46 (0.27)
% Change from baseline	5	-2.68 (9.19)	4	-0.79 (15.75)

1. patients initially randomized to miglustat monotherapy
2. patients initially randomized to Imiglucerase or Combination

Table 15 - Long-term blood count changes up to 24 months of Miglustat treatment after Imiglucerase withdrawal

	Hemoglobin concentration (g/dL)		Platelet count (x 10^9 /L)	
Study OGT 918-004	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Baseline	31	12.75 (1.46)	31	171.7 (86.5)
6 months	29	12.40 (1.15)	29	147.6 (78.6)
% Change from baseline	29	-2.14 (5.51)	29	-12.0 (14.2)
12 months	28	12.38 (1.24)	28	146.6 (77.5)
% Change from baseline	28	-2.48 (5.59)	28	-14.8 (14.9)
18 months	20	12.76 (1.43)	20	153.2 (77.9)
% Change from baseline	20	-1.63 (7.69)	20	-16.9 (17.6)

	Hemoglobin concentration (g/dL)		Platelet count (x 10^9 /L)	
24 months[1]	6	12.97 (1.09)	6	144.2 (37.4)
% Change from baseline	6	1.49 (5.30)	6	-7.8 (19.6)

1. patients initially randomized to miglustat monotherapy

In patients who had evidence of stable Type 1 Gaucher disease when they were withdrawn from imiglucerase, maintained disease control was seen in the majority of patients during treatment with miglustat monotherapy for up to 24 months. In these patients maintenance of stable disease on miglustat monotherapy was observed in 11/15 patients (73%) for a mean treatment duration of 19 months. Four patients developed signs that could be related to loss of disease control (increase in organ volume and/or reduction in platelet or hemoglobin values). Patients who had not been fully stabilized on imiglucerase had a lower probability of a successful outcome on miglustat. Irrespective of the degree of disease stability at time of imiglucerase withdrawal, no patient showed rapid deterioration of Type 1 Gaucher disease following the switch to miglustat monotherapy.

Bone manifestations of Type 1 Gaucher disease were evaluated in 3 open-label clinical studies (Study OGT 918-001; Study OGT 918-004; Study OGT 918-005) in patients treated with miglustat 100 mg three times daily for up to 2 years (n = 72). In a pooled analysis, mean bone mineral density Z-scores at the lumbar spine and femoral neck increased significantly from baseline ($p<0.001$) and this effect was evident as early as 6 months after the initiation of treatment (see Table 16). Bone mineral density increased also in splenectomised patients and in patients with osteoporosis. There were no events of bone crisis, avascular necrosis or fracture during the treatment period.

Table 16 - Pairwise changes over time in bone mineral density Z-scores at the lumbar spine and the femoral neck (hip) in all patients

			Change from baseline		
Site and time-point	**N**	**Baseline mean (SD)**	**Mean (SE)**	**95% CI**	**p-value**
Lumbar spine					
Month 6	29	-0.83 (1.16)	0.15 (0.06)	0.02–0.27	0.022
Month 12	26	-0.98 (1.17)	0.19 (0.07)	0.05–0.34	0.012
Month 24	14	-1.46 (1.11)	0.21 (0.08)	0.05–0.38	0.015
Last value	47	-1.18 (1.16)	0.21 (0.05)	0.11–0.32	< 0.001
Femoral neck					
Month 6	30	-0.63 (1.43)	0.23 (0.06)	0.12–0.34	< 0.001
Month 12	23	-0.73 (0.96)	0.21 (0.08)	0.04–0.38	0.017
Month 24	13	-0.82 (0.78)	0.18 (0.08)	0.01–0.34	0.039

			Change from baseline		
Site and time-point	**N**	**Baseline mean (SD)**	**Mean (SE)**	**95% CI**	**p-value**
Last value	43	-0.76 (1.27)	0.27 (0.06)	0.15–0.38	< 0.001

Niemann-Pick Type C Disease

Table 17 - Summary of patient demographics for clinical trials in Niemann Pick Type C disease

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
OGT 918-007	Open-label, comparative, controlled study	Miglustat 200 mg three times a day oral Duration: 12 months	Miglustat: 20 No Treatment: 9	24.6 ± 9.1 yrs (12-42)	14 M 15 F
OGT 918-007 (Optional Extended study)	Open-label, non-controlled	Miglustat 200 mg three times a day oral Duration: 12 months (up to 24 months total)	Miglustat: 25	25.0 ± 9.2 yrs (12-42)	14 M 11 F
OGT 918-007 (Optional continued treatment extension period)	Open-label, non-controlled	Miglustat 200 mg three times a day oral Duration: from month 24 to study closure (up to 42 months)	Miglustat: 16	22.6 ± 9.4 yrs (12-42)	9 M 7 F
OGT 918-007 Pediatric sub-study	Open-label, non-controlled	Miglustat 200 mg three times a day oral equivalent according to BSA[1] Duration: 12 months	Miglustat: 12	7.2 ± 2.5 yrs (4-11)	5 M 7 F
OGT 918-007 Pediatric sub-study Optional continued treatment extension	Open-label, non-controlled	Miglustat 200 mg three times a day oral equivalent according to BSA[1] Duration: 12 months (up to 24 months total)	Miglustat: 10	7.2 ± 2.4 yrs (4-11)	4 M 6 F

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
period					
OGT 918-007 Pediatric sub-study Optional continued treatment extension period	Open-label, non-controlled	Miglustat 200 mg three times a day oral equivalent according to BSA[1] Duration: from month 24 to study closure (up to 36 months)	Miglustat: 10	7.2 ± 2.4 yrs (4-11)	4 M 6 F

1. BSA = body surface area

The efficacy of miglustat in Niemman-Pick Type C disease comes from Study OGT 918-007, which was a prospective open-label clinical trial (Table 17), followed by an extension therapy for an average total duration of 3.9 years and up to 5.6 years. In addition, 12 pediatric patients were enrolled in an uncontrolled substudy for an overall average duration of 3.1 years and up to 4.4 years. Among the 40 patients exposed to miglustat in the trial 14 patients were treated for more than 3 years.

The primary endpoint evaluated change from baseline in horizontal saccadic eye movement (HSEM) velocity, expressed as HSEM-α. In miglustat-treated patients a mean improvement (reduction in HSEM-α) compared to baseline was observed versus a deterioration in the No Treatment group. Pediatric patients treated with miglustat also showed improvement from baseline (Table 18).

Table 18 - Change from baseline in HSEM-α up to 12 months, study OGT 918-007

Parameter		Adjusted mean change from baseline (95% CI) Adult/juvenile patients	Estimated treatment difference (95% CI)	Mean change from baseline (95% CI) Pediatric patients

		No Treatment (N = 8)	Miglustat (N = 18)		Miglustat (N = 10)
HSEM-α (ANCOVA with terms for baseline, age, treatment)	Last value[1]	-0.050 (-0.608, 0.509)	-0.376 (-0.746, -0.005)	-0.326 (-1.000, 0.348) p = 0.327	-0.465 (-0.752, -0.178)
HSEM-α (ANCOVA with terms for baseline, center, treatment)	Last value[1]	0.055 (-0.443, 0.553)	-0.463 (-0.796, -0.129)	-0.518 (-1.125, 0.089) p = 0.091	

[1]Last value is the last post-baseline value up to Month 12. Increase from baseline indicates worsening

In a *post hoc* analysis, which excluded patients taking benzodiazepines, known to affect saccadic eye movement velocity, the treatment difference for HSEM-α between miglustat and No Treatment was -0.718 (95% CI -1.349, -0.088, p = 0.028).

Swallowing function was assessed on a rating scale, evaluating the patient's ability to swallow water and food substances of varying consistencies. Better maintenance of swallowing function was observed with miglustat treatment versus No treatment (Relative risk for any deterioration up to Month 12: 0.4 (95% CI 0.13, 1.22, p = 0.17)). Overall, about 80% of adult/juvenile and pediatric patients retained at least stable swallowing at 24 months of miglustat treatment.

Motor disability was assessed with the Hauser Standard Ambulation Index (SAI). Better maintenance of ambulatory function (less deterioration from baseline in mean SAI) was observed with miglustat treatment versus No treatment during the 12-month controlled study in adult/juvenile patients [miglustat: 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)]. After 2 years of miglustat treatment, two-thirds of adult/juvenile and pediatric patients maintained at least stable ambulatory ability.

The assessment of cognitive ability, measured through change from baseline in the Folstein Mini-Mental Status Examination (MMSE) score in adult/juvenile patients, also showed a difference in favour of miglustat during the controlled 12-month phase of study OGT 918-007 [miglustat: 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)].

The data from treatment with miglustat of pediatric (4-12 years of age) patients with Niemann-Pick Type C disease fully corroborate the findings in the controlled study in juvenile and adult patients.

Additional data to support efficacy of miglustat come from a retrospective survey comprising a case series of 66 patients with Niemann-Pick Type C disease treated with miglustat for a mean duration of 1.5 years, following a mean pre-treatment observation of 3.1 years. This data set also included pediatric, juvenile and adult patients with an age range of 1 year to 43 years. 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, miglustat was associated with clinically relevant reductions in annualized progression rate, compared with pre-treatment.

14.3 Comparative Bioavailability Studies

Comparative Bioavailability Studies
Randomized, blinded, single dose 2-way crossover comparative bioavailability study of Sandoz Miglustat (miglustat, Sandoz Canada Inc.) 100 mg capsules versus Zavesca® (miglustat, Actelion Pharmaceuticals Canada Inc.,) 100 mg capsules in 30 healthy male (28) and female (2) volunteers aged 20-52 years under fasting conditions. Bioavailability data were measured and the results are summarized in the following table.

Miglustat (1 x 100 mg) From measured data Geometric LS Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric LS Means	90% Confidence Interval
AUC_{0-T} (ng·h/mL)	9906.3 10115.8 (20.6)	10317.9 10561.4 (22.3)	96.0	91.5 - 100.7
$AUC_{0-\infty}$ (ng·h/mL)	10111.2 10320.6 (20.4)	10523.6 10767.8 (22.1)	96.1	91.6 - 100.7

Miglustat (1 x 100 mg) From measured data Geometric LS Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric LS Means	90% Confidence Interval
C_{max} (ng/mL)	1078.4 1108.4 (23.4)	1096.1 1135.5 (26.4)	98.4	92.6 - 104.5
T_{max}§ (h)	2.50 (1.00 – 5.00)	2.50 (0.75 – 5.00)		
$T_{½}$€ (h)	8.92 (10.0)	8.71 (8.4)		

* Sandoz Miglustat 100 mg capsules (manufactured for Sandoz Canada Inc.)
† Zavesca® 100 mg capsules (manufactured by Actelion Pharmaceuticals Canada Inc., and purchased in Canada)
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV%) only

15 MICROBIOLOGY

No microbiological information is required for this drug product

16 NON-CLINICAL TOXICOLOGY

General Toxicology

The main effects common to all species tested (mouse, rat, rabbit, dog and monkey) were weight decreases in body weight gain and food consumption, accompanied by diarrhea, and, at higher doses, damage to the gastrointestinal mucosa (erosions and ulceration). Further, effects seen in animals at doses that result in exposure levels moderately higher than the clinical exposure level were: changes in lymphoid organs in all species tested, transaminase changes, vacuolation of thyroid and pancreas, cataracts, nephropathy, and myocardial changes in rats. These findings were considered to be secondary to deterioration of study animals and are not relevant for human risk assessment.

No behaviorally or neuro-toxicologically significant effects of miglustat were observed in rats following oral administration of miglustat at 60, 180 and 420 mg/kg/day for 26 weeks. In particular, specific neuropathological examination showed no treatment-related effects in the brain, spinal cord, peripheral nerves, nerve roots, or dorsal root ganglia.

Table 19 - Single-Dose Toxicity Studies

Species	Method of Administration	Doses (mg/kg)	Observed Max. Non-Lethal Dose
Mouse	Gavage	2800, 5000	5000 mg/kg
Mouse	Gavage	1250, 2500, 5000[1]	5000 mg/kg
Rat	24 hour iv infusion	10.6, 31.8, 53.6, 106 mg/kg/hr	106 mg/kg/hr
Noteworthy Findings:			
Mouse	**5000 mg/kg** **5000, 2800 mg/kg**	**No deaths.** appeared unkempt. soft stools observed on Day 2.	
Rat	**106 mg/kg** **106, 53.6 mg/kg**	**No deaths.** signs of swollen limbs during first 4 hours of infusion body weight gain significantly decreased	

1. Two doses separated by 24 hours for each dosage level

Table 20 - Short-Term Multiple-Dose Toxicity Studies

Species	Method of Administration	Doses (mg/kg/day); Duration
Mouse	Gavage	240, 1200, 2400; 2 weeks
Rat	Gavage	180, 840, 4200; 4 weeks
Rabbit	Gavage	60, 180; 7 days
Dog	Capsule	35, 70, 105, 140; 4 weeks 85, 165, 495, and 825; 2 weeks
Monkey	Gastric intubation	165, 495, 1650; 4 weeks
Noteworthy Findings:		

Species	Method of Administration	Doses (mg/kg/day); Duration
Mouse	**All doses:** **2400, 1200 mg/kg/day**	weight loss; significantly increased spleen weight. significantly increased liver and thymus weights.
Rat	**4200 mg/kg/day** **4200, 840 mg/kg/day** **840, 180 mg/kg/day** **840 mg/kg/day**	(all animals died/sacrificed in extremis due to/associated with severe diarrhea); swollen limbs; increased mitotic figures in cecal epithelium; depleted goblet cells throughout intestine; villus atrophy in jejunum and ileum; prostate atrophy; lymphocytic depletion in spleen, thymus and lymph nodes. watery stool; ventral staining; swollen abdomen; decreased body weight, body weight gain, and food consumption (severe in 4200, sporadic in 840); hemorrhage in stomach; atrophy of pituitary pars distalis; bone marrow hypocellularity; decreased spermatogenesis in testis; hypospermia in epididymis; atrophy of seminal vesicles. increased urinary calcium; significantly lower platelet values; hypospermia in epididymis. significantly increased serum AST, ALT activities, glucose and calcium concentration (females); decreased creatinine, total protein, total globulin (males), and albumin (females); decreased thymus, spleen, ovary and uterus weights and ratios.
Rabbit	**180, 60 mg/kg/day** **180 mg/kg/day** **60 mg/kg/day**	reduced fecal output; decreased body weight and food consumption. red thymus and subcutaneous tissue; clear cysts in kidney; red pancreatic nodule. red depressed areas of stomach; mottled kidneys.
Dog[1]	**All doses:** **140, 105, 70 mg/kg/day** **140, 105 mg/kg/day** **105, 70 mg/kg/day** **105 mg/kg/day** **≥ 495 mg/kg/day** **≥ 85 mg/kg/day**	hyperaemia of small and large intestines; melena/bloody contents in bowel (with occasional acute inflammatory infiltrate). decreased hematocrit, hemoglobin and RBC count. decreased body weight and food consumption**.** increased AST; decreased hematocrit, hemoglobin and RBC count. one death (black watery stool, dilated pupils, noisy breathing, prostrate prior to death); eye discharge; absent corneal reflexes, red mucoid stool; tremors; favouring of a limb; vomitus; soft/watery/mucoid stools. ataxia, diminished/absent pupillary, palpebral, or

Species	Method of Administration	Doses (mg/kg/day); Duration
		patellar reflexes. gastrointestinal necrosis, inflammation, and hemorrhage.
Monkey	**All doses** **495, 1650 mg/kg/day** **1650 mg/kg/day** **495 mg/kg/day**	dose-related decrease in appetite and body weight gains. significantly decreased albumin; decreased albumin/globulin ratio; significantly increased LDH fractions (LDH1, LDH2, LDH3) and bicarbonate; enlarged and discoloured liver; red and black discolouration of mucosal surface of jejunum, caecum and colon; absence of rugae and sloughing mucosa in stomach. 5 deaths (4 died/sacrificed moribund, 1 found dead 3 days after end of dosing); soft and bloody stool; diarrhea; emesis; hypoactivity; appetite changes; depression; significantly increased platelet counts; significantly decreased sodium and chloride; increased potassium. 3 deaths (found dead on Days 7, 13 and 18); soft stool; diarrhea; dehydration; depression.

1. Dosing regimen had no effect on vomitus or stool changes. Neither regimen nor escalation provided evidence of tolerance.

Table 21 - Long-Term Multiple-Dose Toxicity Studies

Species	Method of Administration	Doses (mg/kg/day); Duration
Mice	Gavage	100, 420, 840; 13 weeks
Rat	Gavage	180, 420, 840, 1680[1]; 52 weeks 300, 600,1200; 26 weeks
Monkey	Gavage	750, 2000; 52 weeks
Noteworthy Findings:		

Species	Method of Administration	Doses (mg/kg/day); Duration
Mouse	**420 & 840 mg/kg/day**	lymphocytolysis in thymus significantly increased.
Rat	**180, 420 & 840 mg/kg/day**	elevated white cell counts (due to increased neutrophils and lymphocytes); low gamma globulin values; high phosphorus, calcium, and potassium; high urine calcium values; treatment and dose-related increases in spermatogenesis, interstitial oedema, and atrophy of seminiferous tubules (microscopic).
	420, 840 mg/kg/day	decreased platelet counts; inhibited body weight gain and food consumption; high serum AST values; soft and/or small testes.
	840 mg/kg/day	low total protein and albumin; equatorial cataracts.
	420 mg/kg/day	transitory equatorial cataracts.
	180 mg/kg/day	slightly inhibited body weight gain.
	1200 mg/kg/day	gastrointestinal necrosis, inflammation, and hemorrhage.
Monkey	**≥ 750 mg/kg/day**	gastrointestinal necrosis, inflammation, and hemorrhage.

1. Dosing terminated during Week 10 due to high mortality rate - results for this dose group are therefore not shown.

Carcinogenicity

Administration of miglustat to male and female Sprague Dawley rats for 100 weeks at dose levels of 30, 60 and 180 mg/kg/day resulted in an increased incidence of testicular interstitial cell (Leydig cell) hyperplasia and interstitial cell adenomas in male rats at all dose levels. A No Observed Effect Levels (NOEL) was not established and the effect was not dose dependent. Mechanistic studies revealed that decreased prolactin production may contribute to Leydig cell hyperplasia and adenomas in the rat. This is a rat- specific mechanism, which is considered to be of low relevance for humans. There were no significant increases in tumors in female rats or in male rats at other sites. Interstitial cell adenomas in rats with non-genotoxic compounds are generally considered to be of low relevance to humans.

Administration of miglustat to 300 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, hyperplastic and, occasionally, neoplastic lesions in the large intestine in both sexes. Neoplasms were found in 0/50, 0/49, 1/50, 2/50 and 3/50 males and 0/50, 0/49, 0/49, 1/50 and 2/49 females treated at 0, 0, 210, 420 and 840/500 mg/kg/day, respectively. Trend tests were significant for males and females (males: p=0.005, females: p=0.017) whereas group-wise comparisons revealed a significant increase in incidence for males at the top dose of 840/500 mg/kg/day, only (p=0.007). Since intestinal effects were observed

after oral but not intravenous administration of miglustat, the local exposure (in mg/kg/day) is considered to be relevant rather than the systemic exposure. The doses in this study corresponded to 49, 98 and 196/116 times the recommended human dose at 100 mg three times a day. Carcinomas in the large intestine occurred occasionally at all doses with a statistically significant increase in the high dose group. The relevance of these findings to humans cannot be excluded. There was no drug-related increase in tumor incidence in any other organ.

Genotoxicity

Miglustat was not mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays including the bacterial reverse mutation (Ames), chromosomal aberration (in human lymphocytes), gene mutation in mammalian cells (Chinese Hamster Ovary), and mouse micronucleus assays.

Table 22 - Genotoxicity Studies – In-Vitro

Test	Study Overview	Positive Controls	Doses (mcg/plate)
Bacterial Reverse Mutation Test	Two independent mutation tests (Ames plate incorporation and pre-incubation) were performed in the presence and absence of S-9 mix metabolic activation system (derived from β-naphthoflavone and sodium phenobarbitone treated rats).	SALMONELLA TYPHIMURIUM, strains TA1535, TA1537, TA98 and TA100 ESCHERICIA COLI, strain WP2 uvrA	8, 40, 200, 1000, 5000
Mammalian Cell Cytogenic Test: Human Lymphocyte	Two experiments were performed in which human lymphocytes from 2 donors were treated with miglustat or positive controls in the presence and absence of S-9. In the first experiment, the dosing period was 3 hours and harvesting was approximately 1.5 cell cycles after the start of dosing. In the second experiment, treatment was for 3 hours in the presence of S-9 and 1.5 cell cycles in the absence of S-9. Two harvest times were used: 1.5 cell cycles and 24 hours later.	Mitomycin C, cyclophosphamide	500, 2500, 5000 mcg/ml

Test	Study Overview	Positive Controls	Doses (mcg/plate)
Results/Conclusion:			
Bacterial Reverse Mutation Test	Statistically significant increases in revertant numbers were detected in the plate incorporation test using strain WP2 uvrA at 8 mcg/plate in the presence of S-9 and in the pre-incubation test using TA100 at 40 mcg/plate without S-9. No dose response was associated with either of these increases and they are not thought to be of biological significance. No other statistically significant increase in revertant numbers was seen with any strain at any dose in the presence or absence of S-9. Miglustat was not a mutagen in the presence or absence of S-9 under the conditions of this test.		
Mammalian Cell Cytogenic Test	Miglustat was not clastogenic under the conditions of this test.		

Table 23 - Genotoxicity Studies – In-Vivo

Species	Study Overview	Doses (mg/kg/day); Route; Regimen
Mouse	Miglustat was investigated for the potential to induce micronuclei in the bone marrow polychromatic erythrocytes of mice. The animals were sacrificed 24 hours after the second dose was administered and bone marrow smears were prepared for micronucleus analysis.	1250, 2500, 5000; oral (gavage); twice daily, 24 hours apart. Animals were sacrificed 24 hours after second dose.
Results/Conclusion: No significant increase in the micronucleus induction rate was observed at any dosage level relative to the vehicle control response. These results support a conclusion that miglustat does not induce micronuclei in bone marrow cells of mice under the conditions of this assay.		

Similar results to those of the Bacterial Reverse Mutation Test were obtained from a mutagenicity study utilizing the Chinese Hamster Ovary (CHO)/HGPRT Mutation Assay.

Reproductive and Developmental Toxicology:

In pregnant rabbits given miglustat by oral gavage at doses of 15, 30, 45 mg/kg/day during gestation days 6-18 (organogenesis), maternal death and decreased body weight gain were observed at 15 mg/kg/day (systemic exposures less than the human therapeutic systemic exposure, based on body surface area comparisons).

Table 24 – Reproductive Toxicity Studies

Species	Method of Administration	Doses (mg/kg/day); Duration
Rat	Gavage	20, 60, 180; Males - 2 weeks prior to mating until 5 weeks after; Females: 2 weeks prior to mating until Day 7 post-partum
Rat	Gavage	20, 60, 180; Males: 14 or 70 days prior to mating and during mating
Rat	Gavage	60; Males: 42 days prior to mating, during mating until necropsy 1 week after mating
Rat	Gavage	20, 60, 180; Females: 15 days prior to mating until day 17 of pregnancy
Rat	Gavage	20, 60, 180; Females: from gestation day 6 through lactation (postpartum day 20)
Rabbits	Gavage	15, 30, 45 Females: during gestation days 6-18 (organogenesis)

Noteworthy Findings:		
Males	**180, 60, 20 mg/kg/day**	reduced sperm motility and concentration; decreased sperm actual path velocity; sperm morphology changes (reduced normal sperm, increased headless and reduced hook sperm); reduced weight of cauda epididymis.
	180, 60 mg/kg/day	increased reduced hook sperm; increased miscellaneous sperm abnormalities.
	180 mg/kg/day	possible effect on fertility after 4 and 13 weeks of treatment.
	60, 20 mg/kg/day	reduced sperm concentration and straight line velocity.
	60 mg/kg/day	reduced fertility (caused increase in number of unfertilized and fragmenting eggs; seminiferous tubule and testicular atrophy/degeneration
	20 mg/kg/day	decreased spermatogenesis with altered sperm morphology and motility and decreased fertility. Decreased spermatogenesis was reversible following 6 weeks of drug withdrawal.
Female Rats	**180, 60, 20 mg/kg/day**	reduced corpora lutea and implantations; increased pre-implantation loss (following 12 or 13 weeks treatment); decreased live births; decreased pup body weights.
	180, 60 mg/kg/day	increased duration of gestation; delayed parturition; increased early embryo fetal deaths; increased post-implantation loss; increased placental weight.
	180 mg/kg/day	decreased body weight gain from Day 12 of gestation; decreased fetal weight and litter size; increased placental weight.
	60 mg/kg/day	decreased number of pups. There was a treatment related increase in mean male and female pup body weight throughout lactation. This was considered to be a result of the small litter sizes and increased duration of gestation noted in the treated groups. The effect of treatment on the mean number of corpora lutea, implantations, pre-implantation loss and sperm morphology at all dose levels did not follow a dose-related pattern but resembled a 'bell-shaped curve'. At the mating 6 weeks following cessation of treatment, pregnancy parameters had returned to within normal ranges. Thirteen weeks after cessation of treatment, there was no effect of treatment on sperm morphology.

Female Rabbits	**15 mg/kg/day**	maternal death; decreased body weight gain

Special Toxicology:

Table 25 - Local Tolerance Tests

Species	Study Overview	Dose; Route; Regimen
Mouse	The mouse ear swelling test was conducted to assess the sensitisation potential of miglustat. Mice received an intradermal injection of a 1:1 emulsion of Freund's Complete Adjuvant and water on each side of the abdominal midline on Study Day 1.	10%, 30% (w/v); dermal (solution); 10% applied to abdomen on Days 1, 2, 3 and 4 and 30% applied to ears on Day 11.
Rabbit	OGT 918 was tested for primary dermal irritation potential in rabbits. Each of three rabbits was simultaneously exposed to duplicates of four different treatments (8 dermal sites/rabbit) on the skin of the back and flanks.	250 mg/site (miglustat); dermal (solution); applied for approximately 24 hours using Hill Top chamber dermal delivery system.
Results/Conclusion:		
Mouse	There were no positive or equivocal responses. Miglustat did not cause sensitisation at the concentration tested in this study.	
Rabbit	Miglustat was mildly irritating.	

17 SUPPORTING PRODUCT MONOGRAPHS

Zavesca® capsules 100 mg, submission control number: 255321, Product Monograph, Janssen Inc. January 17, 2022

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr Sandoz Miglustat
migLUstat capsules

Read this carefully before you start taking **Sandoz Miglustat** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Sandoz Miglustat**.

What is Sandoz Miglustat used for?
Sandoz Miglustat is used for:

- the treatment of mild to moderate Type 1 Gaucher disease in adults who cannot use imiglucerase, or enzyme replacement therapy.
- slowing the progression of some of the neurologic symptoms in adults and children 4 years of age and older with Niemann-Pick Type C disease (affecting the brain and nervous system).

How does Sandoz Miglustat work?
Sandoz Miglustat prevents an enzyme called glucosylceramide synthase from working. This reduces the production of fatty substances called glycosphingolipid glucosylceramide in cells.

Type I Gaucher disease is a condition in which there is a build-up of glucosylceramide in certain cells of the body's immune system called macrophages. This results in liver and spleen enlargement, changes in the blood, and bone disease.

In Niemann-Pick Type C disease, glycosphingolipids (fats) build-up in cells in the brain. This can result in problems with eye movement, eye sight (vision), balance, swallowing, speech, and memory, and in seizures (fits).

What are the ingredients in Sandoz Miglustat?
Medicinal ingredients: Miglustat

Non-medicinal ingredients: gelatin, magnesium stearate, povidone, sodium starch glycolate, and titanium dioxide

Sandoz Miglustat comes in the following dosage forms:
Capsule: 100 mg

Do not use Sandoz Miglustat if:

- you are allergic to miglustat or to any of the non-medicinal ingredients in Sandoz Miglustat or any component of the container (see What are the ingredients in Sandoz Miglustat?).
- you are pregnant or planning to get pregnant. Sandoz Miglustat may harm your unborn baby.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Sandoz Miglustat. Talk about any health conditions or problems you may have, including if you:

- have or have had kidney problems
- have liver problems
- have stomach or intestine problems, including inflammatory bowel disease (IBD)
- have or have had cataracts (clouding of the lens of your eye)

Other warnings you should know about:
Sandoz Miglustat should only be prescribed by a healthcare professional experienced in the management of patients with Gaucher disease or Niemann-Pick Type C disease.

Pregnancy, Breastfeeding and Fertility:

Female Patients:

- You must not take Sandoz Miglustat if you are pregnant or planning to become pregnant. Sandoz Miglustat can harm your unborn baby. Your healthcare professional will make sure you are not pregnant before you start taking Sandoz Miglustat.
- If you are able to get pregnant you must use an effective method of birth control while you are taking Sandoz Miglustat.
- You should not breastfeed while you are taking Sandoz Miglustat. It is not known if Sandoz Miglustat passes into breastmilk.

Male Patients:

- You should not father a child while taking Sandoz Miglustat and for three months after taking your last dose.
- You must use effective birth control while you are taking Sandoz Miglustat and for 3 months after your last dose. Your female partner should also use an effective method of birth control while you are taking Sandoz Miglustat and for 3 months after your last dose.
- Sandoz Miglustat can affect your sperm and reduce your fertility.

Blood Tests and Monitoring: Sandoz Miglustat can cause abnormal blood test results. Your healthcare professional will decide when to do blood tests and will interpret the results. They will also monitor the health of your spleen and liver. You should have a neurological exam, to check the health of your brain and nerves before you start taking Sandoz Miglustat. This will be repeated by your healthcare professional periodically during treatment.

Driving and Operating Machinery: Sandoz Miglustat may cause dizziness. Give yourself time after taking Sandoz Miglustat to see how you feel before driving a vehicle or using machinery.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Sandoz Miglustat:

- There are no known relevant interactions at this time.

How to take Sandoz Miglustat:

- Always take Sandoz Miglustat exactly as your heathcare professional has instructed you. You should check with your heathcare professional if you are unsure.

- Your healthcare professional will decide how long you should take Sandoz Miglustat.
- Your healthcare professional might give you a lower dose if you have kidney problems.
- Sandoz Miglustat capsules should be swallowed whole with water.
- Sandoz Miglustat can be taken with or without food. Your risk of diarrhea may be reduced if you take Sandoz Miglustat between meals.

Usual dose:

Type 1 Gaucher disease:

- **Adults 18 years of age and older:** 100 mg three times daily taken at regular intervals.

Niemann-Pick Type C disease:

- **Adults and adolescents 12 to 17 years of age:** 200 mg three times daily.
- **Children 4 to 12 years old:** Your healthcare professional will decide on the correct dose for your child.

Overdose:

If you think you, or a person you are caring for, have taken too much Sandoz Miglustat, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed dose:

If you forget to take a dose of Sandoz Miglustat, do not take another dose to make up for the missed dose. Take your next dose at the usual time.

What are possible side effects from using Sandoz Miglustat?

These are not all the possible side effects you may have when taking Sandoz Miglustat. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- weight loss
- loss of appetite
- dry mouth
- gas (flatulence)
- stomach pain
- indigestion
- nausea
- constipation
- headache
- dizziness, vertigo
- fatigue
- generalized weakness
- flu-like symptoms
- vision changes
- muscle cramps or spasms

- memory problems

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Diarrhea		✓	
COMMON			
Neurological problems: tingling, numbness or pain, loss of reflexes, new tremors or worsening of existing tremors in the hands		✓	
Thrombocytopenia (low levels of platelets in the blood): increased bleeding or bruising, rash with reddish-purple spots, bleeding from the nose or gums, blood in urine or stool		✓	
Convulsions: seizures or fits with or without loss of consciousness			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at room temperature between 15-30°C
- Store in the original container
- Do not use after the expiry date stated on the container
- Keep out of the sight and reach of children

If you want more information about Sandoz Miglustat:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.sandoz.ca, or by calling 1-800-361-3062.

This leaflet was prepared by Sandoz Canada Inc.

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