PACKAGE INSERT

ZAVESCA®

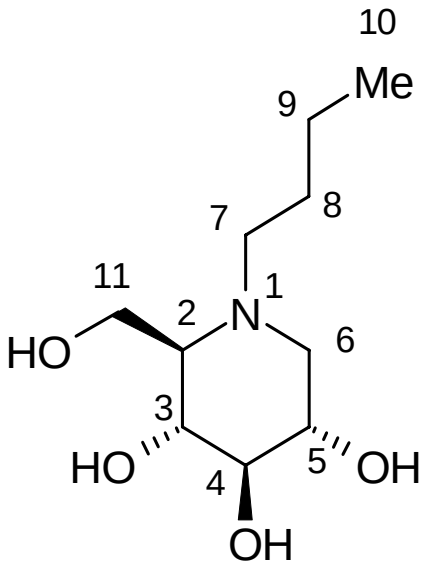
[miglustat]

Capsules, 100mg

DESCRIPTION

ZAVESCA® (miglustat capsules, 100mg) is an inhibitor of the enzyme glucosylceramide synthase, which is a glucosyl transferase enzyme responsible for the first step in the synthesis of most glycosphingolipids. ZAVESCA® is an N-alkylated imino sugar, a synthetic analog of D-glucose.

The chemical name for miglustat is 1,5-(butylimino)-1,5-dideoxy-D-glucitol with the chemical formula $C_{10}H_{21}NO_4$ and a molecular weight of 219.28.



Miglustat is a white to off-white crystalline solid and has a bitter taste. It is highly soluble in water (>1000mg/mL as a free base).

ZAVESCA® is supplied in hard gelatin capsules each containing 100 mg miglustat for oral administration. Each ZAVESCA® 100 mg capsule also contains sodium starch glycollate, povidone (K30), and magnesium stearate. Ingredients in the capsule shell include gelatin and titanium dioxide, and the shells are printed with edible ink consisting of black iron oxide and shellac.

CLINICAL PHARMACOLOGY

Background

Type 1 Gaucher disease is caused by a functional deficiency of glucocerebrosidase, the enzyme that mediates the degradation of the glycosphingolipid glucosylceramide. The failure to degrade glucosylceramide results in the lysosomal storage of this material within tissue macrophages leading to widespread pathology. Macrophages containing stored glucosylceramide are typically found in the liver, spleen, and bone marrow and occasionally in lung, kidney, and intestine. Secondary hematologic consequences include severe anemia and thrombocytopenia in addition to the characteristic progressive hepatosplenomegaly. Skeletal complications include osteonecrosis and osteopenia with secondary pathological fractures. Enzyme replacement therapy is the standard of care for most patients who require treatment for type 1 Gaucher disease.

Mode 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. The goal of treatment with ZAVESCA® is 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). *In vitro* and *in vivo* studies have shown that miglustat can reduce the synthesis of glucosylceramide-based glycosphingolipids. In clinical trials, ZAVESCA® improved liver and spleen volume, as well as hemoglobin concentration and platelet count.

Pharmacokinetics

Absorption

After a 100 mg oral dose, the time to maximum observed plasma concentration of miglustat (t_{max}) ranged from 2 to 2.5 hours in Gaucher patients. Plasma concentrations show a biexponential decline, characterized by a short distribution phase and a longer elimination phase. The effective half-life of miglustat is approximately 6 to 7 hours, which predicts that steady-state will be achieved by 1.5 to 2 days following the start of three times daily dosing.

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

Co-administration of ZAVESCA® with food results in a decrease in the rate of absorption of miglustat (maximum serum concentration [C_{max}] was decreased by 36% and t_{max} delayed 2 h) but has no statistically significant effect on the extent of absorption of miglustat (area-under-the-plasma-concentration curve [AUC] was decreased by 14%).

The mean oral bioavailability of a 100-mg miglustat capsule is about 97% relative to an oral solution administered under fasting conditions.

Distribution

Miglustat does not bind to plasma proteins. Mean apparent volume of distribution of miglustat is 83-105 liters in Gaucher patients, indicating that miglustat distributes into extravascular tissues.

Elimination

The major route of excretion of miglustat is renal. Miglustat is excreted unchanged in the urine. Renal impairment has a significant effect on the pharmacokinetics of miglustat resulting in increased systemic exposure of miglustat in such patients. There is no evidence that miglustat is metabolized in humans.

Special Populations

Gender

There was no statistically significant gender difference in miglustat pharmacokinetics, based on pooled data analysis.

Race

Ethnic differences in miglustat pharmacokinetics have not been evaluated in Gaucher patients. However, apparent oral clearance of miglustat in patients of Ashkenazi Jewish descent was not statistically different to that in others (1 Asian and 15 Caucasians), based on a cross-study analysis.

Hepatic Insufficiency

No studies have been performed to assess the pharmacokinetics of miglustat in patients with hepatic impairment, since miglustat is not metabolized in the human liver.

Renal Insufficiency

Limited data in patients with Fabry disease and impaired renal function indicate that clearance (CL/F) of miglustat decreases with decreasing renal function. While the number of subjects with mild and moderate renal impairment was very 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 dosing of miglustat in such patients dependent upon creatinine clearance levels (see **DOSAGE AND ADMINISTRATION**).

Data in severe renal impairment are limited to two patients with creatinine clearances in the range 18-29 mL/min and cannot be extrapolated below this range. These data suggest

a decrease in CL/F by at least 70% in patients with severe renal impairment. Treatment with miglustat in patients with severe renal impairment is therefore not recommended (see sections on **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Drug Interactions (See also PRECAUTIONS, Drug Interactions)

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

Drug interaction between ZAVESCA® (miglustat 100 mg orally three times daily) and Cerezyme® (imiglucerase; 7.5 or 15 U/kg/day) was assessed in Cerezyme stabilized patients after one month of co-administration. There was no significant effect of Cerezyme on pharmacokinetics of miglustat, with the co-administration of Cerezyme and miglustat resulting in a 22% reduction in C_{max} and a 14% reduction in the AUC for miglustat. While ZAVESCA® appeared to increase the clearance of imiglucerase by 70%, these results are not conclusive because of the small number of subjects studied and because patients took variable doses of Cerezyme (see **PRECAUTIONS, Drug Interactions**).

Concomitant therapy with loperamide during clinical trials did not appear to significantly alter the pharmacokinetics of miglustat.

Clinical Studies

The efficacy of ZAVESCA® in type 1 Gaucher disease has been investigated in two open-label, uncontrolled studies and one randomized, open-label, active-controlled study with enzyme replacement given as Cerezyme. Patients who received ZAVESCA® were treated with doses ranging from 100 to 600 mg a day, although the majority of patients were maintained on doses between 200 to 300 mg a day. Efficacy parameters included the evaluation of liver and spleen organ volume, hemoglobin concentration, and platelet count. A total of 80 patients were exposed to ZAVESCA® during the three studies and their extensions.

Open-Label Uncontrolled Monotherapy Studies

In Study 1, ZAVESCA® 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 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%, a non-significant increase from baseline in mean absolute hemoglobin concentration of 0.26 g/dL and a mean absolute increase from baseline in platelet counts of 8 x 10^9/L (See Tables 1-4).

In Study 2, ZAVESCA® 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 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%. There was a non-significant mean absolute decrease from baseline in hemoglobin concentration of 0.13 g/dL and a non-significant mean absolute increase from baseline in platelet counts of 5 x 10^9/L (See Tables 1-4).

Extension period

Eighteen patients were enrolled in a 12-month extension to Study 1. 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 27%, respectively, and significant mean absolute increases from baseline in hemoglobin concentration and platelet counts of 0.9 g/L and 14 x 10^9/L, respectively (See Tables 1-4).

Sixteen patients were enrolled in a 6-month extension to Study 2. 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%. There were no significant changes in hemoglobin concentrations or platelet counts (See Tables 1-4).

Liver volume results from Studies 1 and 2 and their extensions are summarized in Table 1:

Table 1: Liver Volume Changes in 2 Open-Label Uncontrolled Monotherapy Studies of ZAVESCA® with Extension Phases

	n	Liver Volume	
		Absolute Mean (L) (2-sided 95% CI)	**Percent Mean (%) (2-sided 95% CI)**
Study 1 (starting dose ZAVESCA® 100 mg three times daily)			
Baseline (Month 0)	21	2.39	
Month 12 Change from baseline		-0.28 (-0.38, -0.18)	-12.1% (-16.4, 7.9)
Study 1 Extension Phase			
Baseline (Month 0)	12	2.54	
Month 24 Change from baseline		-0.36 (-0.48, -0.24)	-14.5% (-19.3, 9.7)
Study 2 (ZAVESCA® 50 mg three times daily)			
Baseline (Month 0)	17	2.45	
Month 6 Change from baseline		-0.14 (-0.25, -0.03)	-5.9% (-9.9, -1.9)
Study 2 Extension Phase			
Baseline (Month 0)	13	2.35	
Month 12 Change from baseline		-0.17 (-0.3, -0.0)	-6.2% (-12.0, -0.5)

Spleen volume results from Studies 1 and 2 and their extensions are summarized in Table 2:

Table 2: Spleen Volume Changes in 2 Open-Label Uncontrolled Monotherapy Studies of ZAVESCA® with Extension Phases

	n	Spleen Volume	
		Absolute Mean (L) (2-sided 95% CI)	**Percent Mean (%) (2-sided 95% CI)**
Study 1 (starting dose ZAVESCA® 100 mg three times daily)			
Baseline (Month 0)	18	1.64	
Month 12 Change from baseline		-0.32 (-0.42, -0.22)	-19.0% (-23.7, -14.3)
Study 1 Extension Phase			
Baseline (Month 0)	10	1.56	
Month 24 Change from baseline		-0.42 (-0.53, -0.30)	-26.4% (-30.4, -22.4)
Study 2 (ZAVESCA® 50 mg three times daily)			
Baseline (Month 0)	11	1.98	
Month 6 Change from baseline		-0.09 (-0.18, -0.01)	-4.5% (-8.2, -0.7)
Study 2 Extension Phase			
Baseline (Month 0)	9	1.98	
Month 12 Change from baseline		-0.23 (-0.46, 0.00)	-10.1% (-20.1, -0.1)

Hemoglobin concentration results from Studies 1 and 2 and their extensions are summarized in Table 3:

Table 3: Hemoglobin Concentration Changes in 2 Open-Label Uncontrolled Monotherapy Studies of ZAVESCA® with Extension Phases

	n	Hemoglobin Concentration	
		Absolute Mean (g/dL) (2-sided 95% CI)	**Percent Mean (%) (2-sided 95% CI)**
Study 1 (starting dose ZAVESCA® 100 mg three times daily)			
Baseline (Month 0)	22	11.94	
Month 12 Change from baseline		0.26 (-0.05, 0.57)	2.6% (-0.5, 5.7)
Study 1 Extension Phase			
Baseline (Month 0)	13	11.03	
Month 24 Change from baseline		0.91 (0.30, 1.53)	9.1% (2.9, 15.2)
Study 2 (ZAVESCA® 50 mg three times daily)			
Baseline (Month 0)	17	11.60	
Month 6 Change from baseline		-0.13 (-0.51, 0.24)	-1.3% (-4.4, 1.8)
Study 2 Extension Phase			
Baseline (Month 0)	13	11.94	
Month 12 Change from baseline		0.06 (-0.73, 0.85)	1.2% (-5.2, 7.7)

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

Platelet count results from Studies 1 and 2 and their extensions are summarized in Table 4:

Table 4: Platelet Count Changes in 2 Open-Label Uncontrolled Monotherapy Studies of ZAVESCA® with Extension Phases

	n	Platelet Count	
		Absolute Mean (10^9/L) (2-sided 95% CI)	**Percent Mean (%) (2-sided 95% CI)**
Study 1 (starting dose ZAVESCA® 100 mg three times daily)			
Baseline (Month 0)	22	76.58	
Month 12 Change from baseline		8.28 (1.88, 14.69)	16.0% (-0.8, 32.8)
Study 1 Extension Phase			
Baseline (Month 0)	13	72.35	
Month 24 Change from baseline		13.58 (7.72, 19.43)	26.1% (14.7, 37.5)
Study 2 (ZAVESCA® 50 mg three times daily)			
Baseline (Month 0)	17	116.47	
Month 6 Change from baseline		5.35 (-6.31, 17.02)	2.0% (-6.9, 10.8)
Study 2 Extension Phase			
Baseline (Month 0)	13	122.15	
Month 12 Change from baseline		14.0 (-3.4, 31.4)	14.7% (-1.4, 30.7)

Open-Label Active-Controlled Study

Study 3 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 Cerezyme for a minimum of 2 years prior to study entry. Patients were randomized 1:1:1 to one of three treatment groups, as follows:

- ZAVESCA® 100 mg three times daily alone
- Cerezyme (patient's usual dose) alone
- ZAVESCA® 100 mg three times daily + Cerezyme (usual dose)

Patients were treated for 6 months, and 33 patients completed the 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 Cerezyme alone group. There were no significant differences between the groups for mean absolute changes in liver and spleen volume and hemoglobin concentration. However, there was a significant difference between the ZAVESCA® alone and Cerezyme alone groups in platelet counts at Month 6, with the ZAVESCA® alone group having a mean absolute decrease in platelet count of 21.6 x 10^9/L and the Cerezyme alone group having a mean absolute increase in platelet count of 10.1 x 10^9/L (see Tables 5-8).

Extension period

Twenty-nine patients were enrolled in a 6-month extension to Study 3. In the extension phase, all 29 patients had withdrawn from Cerezyme and received open-label ZAVESCA® 100 mg three times daily monotherapy. At Month 12, the results showed non-significant decreases in platelet counts from baseline in all three treatment groups (by original randomization). There were significant decreases in platelet counts from Month 6 to Month 12 in the 2 groups originally randomized to treatment with Cerezyme and to combination therapy, and a continued decrease in platelet counts in the group originally randomized to ZAVESCA® alone. There were no significant changes in any treatment group for liver volume, spleen volume, or hemoglobin concentration (see Tables 5-8).

Liver volume results from Study 3 and extension are summarized in Table 5:

Table 5: Liver Volume Changes from Study 3 and Extension Phase

	Cerezyme alone	ZAVESCA® alone	Combination
Study 3	n=11	n=10	n=9
Month 0	1.81	1.58	2.01
Month 6 Change (L)	0.04	-0.05	-0.09
Month 6 % Change	3.6%	-2.9%	-4.9%
Adjusted mean Difference from Cerezyme (95% CI)		-4.5% (-13.2, 4.2)	-8.4% (-16.6, -0.1)
Extension Phase*	n=10	n=8	n=8
Month 0	1.94	1.60	2.04
Month 12 Change (L)	-0.05	-0.01	-0.08
Month 12 % Change	-0.7%	-0.8%	-4.0%

*All patients received ZAVESCA® 100 mg three times daily monotherapy from Month 6 to Month 12

Spleen volume results from Study 3 and extension are summarized in Table 6:

Table 6: Spleen Volume Changes from Study 3 and Extension Phase

	Cerezyme alone	ZAVESCA® alone	Combination
Study 3	n=8	n=7	n=7
Month 0	0.61	0.69	0.76
Month 6 Change (L)	-0.02	-0.03	-0.08
Month 6 % Change	-2.1%	-4.8%	-8.5%
Adjusted % Difference from Cerezyme (95% CI)		-5.8% (-22.1, 10.5)	-6.4% (-21.0, 8.2)
Extension Phase*	n=7	n=6	n=6
Month 0	0.83	0.57	0.84
Month 12 Change (L)	0.04	-0.05	-0.05
Month 12 % Change	1.5%	-6.1%	-4.8%

*All patients received ZAVESCA® 100 mg three times daily monotherapy from Month 6 to Month 12

Hemoglobin concentration results from Study 3 and extension are summarized in Table 7:

Table 7: Hemoglobin Concentration Changes from Study 3 and Extension Phase

	Cerezyme alone	ZAVESCA® alone	Combination
Study 3	n=12	n=10	n=11
Month 0	13.18	12.44	12.38
Month 6 Change (g/L)	-0.15	-0.31	-0.10
Month 6 % Change	-1.2%	-2.4%	-0.5%
Adjusted % Difference from Cerezyme (95% CI)		-1.9% (-6.4, 2.6)	-0.6% (-4.8, 3.5)
Extension Phase*	n=10	n=9	n=9
Month 0	13.39	12.46	12.20
Month 12 Change (g/L)	-0.48	-0.13	-0.13
Month 12 % Change	-3.1%	-1.1%	-0.8%

*All patients received ZAVESCA® 100 mg three times daily monotherapy from Month 6 to Month 12

Platelet count results from Study 3 and extension are summarized in Table 8:

Table 8: Platelet Count Changes from Study 3 and Extension Phase

	Cerezyme alone	ZAVESCA® alone	Combination
Study 3	n=12	n=10	n=11
Month 0	165.75	170.55	152.14
Month 6 Change (10^9/L)	15.29	-21.60	2.73
Month 6 % Change	10.1%	-9.6%	3.2%
Adjusted % Difference from Cerezyme (95% CI)		-17.1% (-32.9, -1.3)	-4.6% (-19.9, 10.7)
Extension Phase*	n=10	n=9	n=9
Month 0	170.05	184.83	136.33
Month 12 Change (10^9/L)	-3.75	-27.39	-12.22
Month 12 % Change	-3.2%	-10.4%	-8.3%

*All patients received ZAVESCA® 100 mg three times daily monotherapy from Month 6 to Month 12

In patients with platelet counts above 150 x 10^9/L at baseline, there were significant decreases in platelet counts at Month 12 in patients randomized to ZAVESCA® treatment.

Summary of clinical studies

Treatment with ZAVESCA® as monotherapy at a starting dose of 100 mg three times daily (dosage range 100 mg once daily to 200 mg three times daily) in adult type 1 Gaucher disease patients who were either treatment naïve or who had not taken enzyme replacement therapy in the previous 6 months resulted in decreases in liver and spleen volume after 12 months of treatment, and increases in platelet counts and hemoglobin concentration after 24 months of treatment. However, in adult type I Gaucher disease

patients who had been treated with enzyme replacement therapy for at least 2 years, switching to ZAVESCA® as monotherapy was associated with decreases in platelet counts after discontinuation of enzyme replacement therapy. Platelet counts also declined after discontinuation of enzyme replacement therapy in patients treated with combination therapy.

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

INDICATIONS AND USAGE

ZAVESCA® 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 (e.g. due to constraints such as allergy, hypersensitivity, or poor venous access).

CONTRAINDICATIONS

ZAVESCA® is contraindicated in patients who have demonstrated hypersensitivity to the active substance or any of the excipients.

Pregnancy Category X

Miglustat may cause fetal harm when administered to a pregnant woman. In female rats given miglustat by oral gavage at doses of 20, 60, 180 mg/kg/day beginning 14 days before mating and continuing through gestation day 17 (organogenesis), decreased live births including complete litter loss and decreased fetal weight was observed in the mid- and high-dose groups (systemic exposures ≥2 times the human therapeutic systemic exposure based on body surface area comparison). In pregnant rats given miglustat by oral gavage at doses of 20, 60, 180 mg/kg/day from gestation day 6 through lactation (postpartum day 20), dystocia and delayed parturition were observed in the mid- and high-dose groups (systemic exposures ≥2 times the human therapeutic systemic exposure, based on body surface area comparison), in addition decreased live births and pup body weights were observed at >20 mg/kg/day (systemic exposures less than the human therapeutic systemic exposure, based on body surface area comparison).

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).

ZAVESCA® is contraindicated in women who are or may become pregnant. If this drug is administered to a woman with reproductive potential, the patient should be apprised of the potential hazard to a fetus.

WARNINGS

Peripheral Neuropathy

Cases of peripheral neuropathy have been reported in patients treated with ZAVESCA®. All patients receiving ZAVESCA® treatment should undergo baseline and repeat neurological evaluations at approximately 6-month intervals. Patients who develop symptoms such as numbness and tingling should have a careful re-assessment of the risk/benefit of ZAVESCA® therapy and cessation of treatment may be considered.

PRECAUTIONS

General

Therapy should be directed by physicians knowledgeable in the management of patients with Gaucher disease.

Tremor

Approximately 30% of patients have reported tremor or exacerbation of existing tremor on treatment. These tremors were described as an exaggerated physiological tremor of the hands. Tremor usually began within the first month of therapy and in many cases resolved between 1 to 3 months during treatment. Dose reduction may ameliorate the tremor usually within days but discontinuation with treatment may sometimes be required.

Diarrhea and Weight Loss

Diarrhea and weight loss were common in clinical studies of patients treated with ZAVESCA®, with approximately 85% and up to 65% of treated patients, respectively, reporting these conditions. Diarrhea appears to be the result of the disaccharidase inhibitory activity of ZAVESCA®, with a resultant osmotic diarrhea. It is unclear if weight loss results from the diarrhea and associated gastrointestinal complaints, a decrease in food intake, or a combination of these or other factors. The incidence of weight loss was most evident in the first 12 months of treatment. The incidence of diarrhea was noted to decrease over time with continued ZAVESCA® treatment, and was noted to result in an increase in the use of anti-diarrheal medications, most commonly loperamide. Patients may be instructed to avoid high carbohydrate content foods during treatment with ZAVESCA® if they present with diarrhea.

Patients with persistent gastrointestinal events that continue during treatment with Zavesca, and who do not respond to usual interventions (e.g. diet modification), should be evaluated to determine whether significant underlying gastrointestinal disease is present. The safety of treatment with Zavesca has not been evaluated in patients with significant gastrointestinal disease, such as inflammatory bowel disease, and continued treatment of these patients with Zavesca should occur only after consideration of the risks and benefits of continued treatment.

Reductions in Platelet Count

In a clinical trial evaluating the use of ZAVESCA for another indication, mild reductions in platelet counts without association with bleeding were observed in some patients; approximately 40% of patients in this trial had low platelet counts(defined as below 150 x 10^9/L) before starting treatment with ZAVESCA..

Male Fertility

Male patients should maintain reliable contraceptive methods while taking ZAVESCA®. Studies in the rat have shown that miglustat adversely affects spermatogenesis and sperm parameters, thereby reducing fertility. Until further information is available, it is advised that before seeking to conceive, male patients should cease ZAVESCA® and maintain reliable contraceptive methods for 3 months thereafter (see **Carcinogenesis, Mutagenesis, and Impairment of Fertility**).

Information for Patients

Patients should be informed of the potential risks and benefits of ZAVESCA® and of alternative modes of therapy. Patients should be advised that diarrhea, gastrointestinal complaints, and weight loss are common side effects of ZAVESCA® therapy, and to adhere to dietary instructions. Patients should also be advised to promptly report any numbness, pain, or burning in the hands and feet, and the development of tremor or worsening in an existing tremor.

Drug Interactions

While co-administration of ZAVESCA® appeared to increase the clearance of Cerezyme by 70%, these results are not conclusive because of the small number of subjects studied and because patients took variable doses of Cerezyme. Combination therapy with Cerezyme (imiglucerase) and ZAVESCA® is not indicated (see **CLINICAL PHARMACOLOGY, Drug Interactions**).

Animal Toxicology

Histopathology findings in the absence of clinical signs in the central nervous system of the monkey (brain, spine) that included vascular mineralization, in addition to mineralization and necrosis of white matter were observed at >750 mg/kg/day (4 times the human therapeutic systemic exposure based on area-under-the-plasma-concentration curve [AUC] comparisons) in a 52-week oral toxicity study using doses of 750 and 2000 mg/kg/d. Vacuolization of white matter was observed in rats dosed orally by gavage at ≥ 180 mg/kg/d (6 times the human therapeutic exposure based on surface area comparisons, mg/m^2) in a 4-week study using doses of 180, 840, and 4200 mg/kg/d. Vacuolization can sometimes occur as an artifact of tissue processing. Findings in dogs included tremor and absent corneal reflexes at 105 mg/kg/day (10 times the human therapeutic systemic

exposure, based on body surface area comparisons mg/m^2) after a 4-week oral gavage toxicity study using doses of 35, 70, 105, and 140 mg/kg/d. Ataxia, diminished/absent pupillary, palpebral, or patellar reflexes were observed in a dog at ≥495 mg/kg/day (50 times the human therapeutic systemic exposure based on body surface area comparisons, mg/m^2), in a 2-week oral gavage toxicity study using doses of 85, 165, 495, and 825 mg/kg/d.

Cataracts were observed in rats at ≥180 mg/kg/day (4 times the human therapeutic systemic exposure, based on AUC) in a 52-week oral gavage toxicity study using doses of 180, 420, 840, and 1680 mg/kg/d.

Gastrointestinal necrosis, inflammation, and hemorrhage were observed in dogs at ≥ 85 mg/kg/day (9 times the human therapeutic systemic exposure based on body surface area comparisons, mg/m^2) after a 2-week oral (capsule) toxicity study using doses of 85, 165, 495, and 825 mg/kg/d. Similar GI toxicity occurred in rats at 1200 mg/kg/day (7 times the human therapeutic systemic exposure, based on AUC) in a 26-week oral gavage toxicity study using doses of 300, 600, and 1200 mg/kg/d. In monkeys, similar GI toxicity occurred at ≥750 mg/kg/day (6 times the human therapeutic systemic exposure based on AUC) following a 52-week oral gavage toxicity study using doses of 750 and 2000 mg/kg/d.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Two year carcinogenicity studies have been conducted with miglustat in CD-1 mice at oral doses up to 500 mg/kg/day and in Sprague Dawley rats at oral doses up to 180 mg/kg/day. Oral administration of miglustat for 104 weeks produced mucinous adenocarcinomas of the large intestine at 210, 420 and 500 mg/kg/day (about 3, 6 and 7 times the recommended human dose, respectively, based on the body surface area) in male mice and at 420 and 500 mg/kg/day (about 6 and 7 times the recommended human dose, respectively, based on the body surface area) in female mice. The adenocarcinomas were considered rare in CD-1 mice and occurred in the presence of inflammatory and hyperplastic lesions in the large intestine of both males and females. In rats, oral administration of miglustat for 100 weeks produced increased incidences of interstitial cell adenomas of the testis at 30, 60 and 180 mg/kg/day (about 1, 2 and 5 times the recommended human dose, respectively, based on the body surface area).

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.

Male rats, given 20 mg/kg/day miglustat by (systemic exposure less than the human therapeutic systemic exposure based on body surface area comparisons, mg/m^2) oral gavage 14 days prior to mating, had decreased spermatogenesis with altered sperm morphology and motility and decreased fertility. Decreased spermatogenesis was reversible following 6 weeks of drug withdrawal. A higher dose of 60 mg/kg/day (2 times

the human therapeutic systemic exposure based on body surface area comparison, mg/m^2) resulted in seminiferous tubule and testicular atrophy/degeneration.

Female rats were given oral gavage doses of 20, 60, 180 mg/kg/day beginning 14 days before mating and continuing through gestation. Effects observed at 20 mg/kg/day (systemic exposure less than the human therapeutic systemic exposure, based on body surface area comparisons) included decreased corpora lutea, increased postimplantation loss, and decreased live births.

Pregnancy Category X. See **CONTRAINDICATIONS** section.

There are no adequate and well-controlled studies of miglustat in pregnant women. ZAVESCA® should not be used during pregnancy.

Labor and Delivery

Studies in pregnant rats exposed to ZAVESCA® during gestation through lactation are associated with dystocia and delayed parturition at systemic exposure 2 times the human therapeutic systemic exposure, based on body surface area comparisons.

Nursing Mothers

It is not known whether miglustat is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from miglustat, ZAVESCA® should not be used in nursing mothers unless the potential benefit justifies the potential risk to the infant. A decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the lactating woman.

Pediatric Use

The safety and effectiveness of ZAVESCA® in pediatric patients have not been established.

In a combined clinical trial safety data set of 45 patients less than 18 years of age exposed to ZAVESCA in indications other than type 1 Gaucher disease, the median weight and height percentiles adjusted for age and gender decreased during the first year of treatment but then stabilized. The mean length of exposure in these studies ranged from 2 to 2.6 years; some pediatric patients were exposed for up to 4 years. However, the effect of ZAVESCA on long-term gain in weight and height in pediatric patients is unclear.

Geriatric Use

Clinical studies of ZAVESCA® did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, and cardiac function and of concomitant disease or other drug therapy.

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. 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.

ADVERSE REACTIONS

The most common serious adverse reaction reported with Zavesca treatment in clinical studies was peripheral neuropathy (see **WARNINGS: Peripheral Neuropathy**).

The most common treatment-emergent adverse events reported in clinical studies with Zavesca were weight loss, diarrhea, and tremor (see **PRECAUTIONS: Tremor, and Diarrhea and Weight Loss**). Other common adverse reactions were flatulence, abdominal pain, headache, and influenza-like symptoms.

The most common adverse reaction requiring intervention was diarrhea (see **PRECAUTIONS: Diarrhea and Weight Loss**). Most episodes of diarrhea were ameliorated by the use of anti-diarrheal medications, and/or the avoidance of high carbohydrate content foods, or were noted to decrease over time with continued Zavesca treatment. The next most common adverse reaction requiring intervention was tremor (see **PRECAUTIONS: Tremor**). In many cases, tremor resolved despite continued Zavesca treatment. Dose reduction of Zavesca may ameliorate tremor, but discontinuation of Zavesca was required in some patients.

The data described below reflect exposure of 80 adult type 1 Gaucher disease patients to Zavesca in two open-label, uncontrolled, monotherapy trials, and one open-label, active-controlled trial. Patients were ages 18 to 69 years at first treatment. The population was nearly evenly distributed by gender.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In two open-label, uncontrolled monotherapy trials, adult type 1 Gaucher disease patients were treated with ZAVESCA® at a starting dose of 100 mg three times daily (dose range 100 to 200 mg three times daily) for up to 12 months in 28 patients [Study 1], or at a dose of 50 mg three times daily for up to 6 months in 18 patients [Study 2]. Table 9 below

enumerates adverse events that occurred during the trials in ≥5% of patients. Reported adverse events have been classified using standard WHOART terms.

Table 9: Adverse Reactions in ≥5% of Patients in Two Open-Label, Uncontrolled Monotherapy Trials of ZAVESCA®

	Incidence of adverse reaction	
	Study 1 (starting dose 100 mg three times daily)	**Study 2 (50 mg three times daily)**
Patients entered in Study (n)	28	18
Body System - Preferred Term	% of patients reporting	% of patients reporting
Gastrointestinal System		
Diarrhea	89	89
Flatulence	29	44
Abdominal Pain	18	50
Nausea	14	22
Vomiting	4	11
Bloating	0	6
Anorexia	7	0
Dyspepsia	7	0
Epigastric pain not food-related	0	6
Metabolic and Nutritional Disorders		
Weight Decrease	39	67
Central and Peripheral Nervous System		
Headache	21	22
Tremor	11	11
Dizziness	0	11
Cramps legs	4	11
Paresthesia	7	0
Migraine	0	6
Vision Disorders		
Visual Disturbance	0	17
Musculoskeletal Disorders		
Cramps	0	11
Platelet, Bleeding, and Clotting Disorders		
Thrombocytopenia	7	6
Reproductive disorders, female		
Menstrual disorder	0	6

In an open-label, active-controlled study (versus Cerezyme; imiglucerase), 36 adult type 1 Gaucher disease patients were treated with ZAVESCA®, Cerezyme, or ZAVESCA® + Cerezyme (Study 3) for up to 12 months. Table 10 enumerates adverse events that occurred during the trial in ≥5% of patients. Reported adverse events have been classified using standard WHOART terms.

Table 10: Adverse Reactions in ≥5% of Patients in Open-Label Active Controlled Study			
	Incidence of adverse reaction		
	ZAVESCA® alone	Cerezyme alone	ZAVESCA® + Cerezyme
Patients entered in Study (n)	12	12	12
Body System - Preferred Term	% of patients reporting	% of patients reporting	% of patients reporting
Gastrointestinal System			
Diarrhea	100	0	83
Abdominal Pain	67	0	58
Flatulence	50	0	42
Constipation	8	0	25
Nausea	8	0	8
Mouth dry	8	0	0
Body as a Whole			
Influenza-Like Symptoms	0	0	8
Pain	0	8	8
Pain legs	0	0	8
Weakness generalized	17	0	8
Abdominal distension	8	0	8
Back pain	8	0	0
Abdominal distension gaseous	8	0	0
Chills	0	0	8
Heaviness in limbs	8	0	0
Metabolic and Nutritional Disorders			
Weight Decrease	67	0	42
Central and Peripheral Nervous System			
Tremor	17	0	33
Dizziness	8	0	25
Cramps legs	8	0	0
Gait unsteady	8	0	0
Numbness localized	0	0	8
Shaking	0	0	8
Psychiatric disorders			
Appetite absent	0	0	8
Jitteriness	0	0	8
Memory loss	8	0	0
Vision Disorders			
Eye abnormality	0	0	8
Visual disturbance	0	0	8
Reproductive disorders, female			
Menstrual irregularity	0	0	8

Overdosage

In the clinical development program for ZAVESCA®, no patient experienced an overdose of study drug. However, ZAVESCA® has been administered at doses of up to 3000 mg/day (approximately 10 times the recommended starting 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.

DOSAGE AND ADMINISTRATION

Instructions for Administration

Therapy should be directed by physicians who are knowledgeable in the management of Gaucher disease.

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

It may be necessary to reduce the dose to one 100 mg capsule once or twice a day in some patients for adverse effects, such as diarrhea or tremor.

Patients with Renal Insufficiency

In patients with mild renal impairment (adjusted creatinine clearance 50-70 mL/min/1.73 m^2), ZAVESCA® administration should commence at a dose of 100 mg twice per day. In patients with moderate renal impairment (adjusted creatinine clearance of 30-50 mL/min/1.73 m^2), ZAVESCA® administration should commence at a dose of one 100mg capsule per day. Use of ZAVESCA® in patients with severe renal impairment (creatinine clearance of <30 mL/min/1.73 m^2) is not recommended.

STORAGE

Store at 20ºC to 25ºC (68ºF to 77ºF). Brief exposure to 15ºC to 30ºC (59ºF to 86º F) permitted (see USP Controlled Room Temperature).

HOW SUPPLIED

ZAVESCA® is supplied in hard gelatin capsules containing 100 mg miglustat. ZAVESCA® 100 mg capsules are white opaque with “OGT 918” printed in black on the cap and “100” printed in black on the body.

ZAVESCA® 100 mg capsules are packed in blister cards. Five blister cards of 18 capsules are supplied in each carton.

NDC 66215-201-90: carton containing 90 capsules.
NDC 66215-201-18: blister card containing 18 capsules

Rx only

Manufactured for:

Actelion Pharmaceuticals US Inc
South San Francisco, CA 94080, US
(650) 624 6900

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Patient Information

ZAVESCA® [zah-VEHS-kah]

(miglustat)

Capsules

Read the Patient information that comes with ZAVESCA® before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your condition or your treatment.

What is ZAVESCA®?

ZAVESCA® is a prescription medicine taken by mouth for adults with mild to moderate type 1 Gaucher disease. ZAVESCA® is used only in people who cannot be treated with enzyme replacement therapy.

It is not known if ZAVESCA® is safe and effective in children under 18 years of age.

Who should not take ZAVESCA®?

Do not take ZAVESCA® if you:

- **are allergic to any of the ingredients in ZAVESCA. See the end of this leaflet for a complete list of ingredients.**
- **are pregnant or may become pregnant while taking Zavesca**

What should I tell my doctor before taking ZAVESCA®?

Before you take ZAVESCA tell your doctor if you:

- have kidney problems
- **are pregnant or plan to become pregnant.** ZAVESCA® may harm your baby. You should use effective birth control while taking ZAVESCA®. **ZAVESCA® may also harm a man's sperm.** All men should use effective birth control during treatment with ZAVESCA® and for 3 months after stopping ZAVESCA®. Do not use ZAVESCA® if you plan to become pregnant, or if your partner can become pregnant. See “Who should not take ZAVESCA?”
- **are breastfeeding.** It is not known if ZAVESCA® passes into your milk and if it can harm your baby. You and your doctor should decide if you will breastfeed or take ZAVESCA®. You should not do both.

- **have any other medical conditions**

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may affect ZAVESCA®. ZAVESCA® may affect other medicines.

Know the medicines you take. Keep a list of the medicines you take and show it to your doctor and pharmacist when you get a new medicine.

How should I take ZAVESCA®?

- Take ZAVESCA® exactly as your doctor has prescribed. Check with your doctor or your pharmacist if you are not sure.
- Take ZAVESCA® at the same time or times each day. Your doctor will prescribe the dose that is right for you.
- Swallow ZAVESCA® capsules whole with water. ZAVESCA® may be taken with or without food.
- If you miss a dose of ZAVESCA®, skip that dose. Take the next ZAVESCA® capsule at the usual time.
- If you take too much ZAVESCA® or overdose, call your doctor or local poison control center right away.

What should I avoid while taking ZAVESCA®?

Do not become pregnant while taking ZAVESCA®. See "What should I tell my doctor before taking ZAVESCA?"

What are the possible side effects of ZAVESCA®?

ZAVESCA® may cause serious side effects including:

- **Problems affecting your nerves (neurologic problems):**

New or worse hand tremors (shaky movements). Tremors may begin within the first month of starting treatment. Sometimes the tremors may go away between 1 to 3 months with continued treatment. Sometimes a lower dose or stopping ZAVESCA® is needed if you develop new or worse hand tremors. Call your doctor if you get new hand tremors while taking ZAVESCA® or if the hand tremors you already have get worse.

- **Numbness and tingling in your hands, arms, legs, or feet (peripheral neuropathy).** Call your doctor right away if you get numbness or tingling in your arms or legs.

Your doctor may test your nerves (neurological exam) before you start ZAVESCA® and during treatment with ZAVESCA.

- **Diarrhea.** Your doctor may give you another medicine (anti-diarrheal) to treat diarrhea if it is a problem for you and may recommend changes to your diet.
- **Weight loss.** You may lose weight when you start treatment with ZAVESCA®.
- **Low Platelet Count.** Your doctor may do blood tests to monitor your blood platelet count.

The most common side effects of ZAVESCA® are:

- Stomach pain
- Gas
- Nausea and vomiting
- Headache
- Muscle and leg cramps
- Dizziness
- Weakness
- Vision problems
- Stomach bloating
- Back pain
- Dry mouth
- Constipation
- Heaviness in arms and legs
- Unsteady walking
- Memory loss
- Decreased appetite
- Heartburn
- Menstrual problems

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the side effects with ZAVESCA®. For more information, ask your doctor or your pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA 1088.

How do I store ZAVESCA®?

- Store ZAVESCA® between 68ºF to 77ºF (20ºC to 25ºC)

Keep ZAVESCA® and all medicines out of the reach of children.

General information about ZAVESCA®

Medicines are sometimes prescribed for conditions that are not mentioned in Patient Information leaflets. Do not use ZAVESCA® for a condition for which it was not prescribed. Do not give ZAVESCA® to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about ZAVESCA®. If you would like more information, talk with your doctor. You can ask you doctor or pharmacist for information about ZAVESCA® that is written for

health professionals. For more information about ZAVESCA® call 1-866-228-3546 or go to www.ZAVESCA.com.

What are the ingredients in ZAVESCA®?

Active ingredient: miglustat
Inactive ingredients: sodium starch glycollate, povidone (K30) and magnesium stearate in the capsule; the capsule shell contains gelatin and titanium dioxide; the edible printing ink contains, black iron oxide and shellac.

What is type 1 Gaucher disease?

Type 1 Gaucher disease is an inherited disease that you get from both your parents. People with type 1 Gaucher disease are missing an enzyme that breaks down a chemical in the body called glucosylceramide. Too much glycosylceramide causes liver and spleen enlargement, changes in the blood, and bone disease. ZAVESCA® may stop glucosylceramide from forming.

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