ZAVESCA- miglustat capsule
Actelion Pharmaceuticals US, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZAVESCA safely and effectively. See full prescribing information for ZAVESCA.

ZAVESCA® (miglustat) capsules, for oral use
Initial U.S. Approval: 2003

INDICATIONS AND USAGE

Zavesca is a glucosylceramide synthase inhibitor indicated as monotherapy for treatment of adult patients with mild/moderate type 1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option (1.1).

DOSAGE AND ADMINISTRATION

- Recommended dosage is 100 mg administered orally three times a day at regular intervals (2.1).
- May reduce dosage to 100 mg once or twice a day in some patients due to tremor or diarrhea (2.1).
- Patients with renal impairment (2.2):

Renal Impairment	Adjusted Creatinine Clearance (in mL/min/1.73 m^2)	Recommendations
Mild	50 – 70	Start dose at 100 mg twice a day
Moderate	30 – 50	Start dose at 100 mg once a day
Severe	<30	Use is not recommended

DOSAGE FORMS AND STRENGTHS

Capsules: 100 mg (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Peripheral neuropathy: Perform baseline and follow-up neurological evaluations at 6 month intervals in all patients (5.1).
- Tremor or exacerbation of existing tremors: Reduce dose to ameliorate tremor or discontinue treatment if tremor does not resolve within days of dose reduction (5.2).
- Diarrhea and weight loss: Evaluate for underlying gastrointestinal disease in patients who do not respond to usual interventions (e.g. diet modification) (5.3).

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5%) diarrhea, weight loss, stomach pain, gas, nausea and vomiting headache including migraine, tremor, leg cramps, dizziness, weakness, vision problems, thrombocytopenia, muscle cramps, back pain, constipation, dry mouth, heaviness in arms and legs, memory loss, unsteady walking, anorexia, indigestion, paresthesia, stomach bloating, stomach pain not related to food, and menstrual changes (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Actelion at 1-866-228-3546 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Co-administration of Zavesca and imiglucerase may lead to increased clearance of imiglucerase (7).

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1).
- Nursing mothers: Discontinue drug or nursing based on importance of drug to mother (8.3).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 2/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Type 1 Gaucher Disease

Zavesca is a glucosylceramide synthase inhibitor indicated as monotherapy 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 allergy, hypersensitivity, or poor venous access).

2 DOSAGE AND ADMINISTRATION

2.1 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. If a dose is missed, the next Zavesca capsule should be taken at the next scheduled time.

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

2.2 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 100 mg capsule per day. Use of Zavesca in patients with severe renal impairment (creatinine clearance < 30 mL/min/1.73 m^2) is not recommended *[*see *Use in Specific Populations (8.6)]*.

3 DOSAGE FORMS AND STRENGTHS

100 mg white opaque hard gelatin capsules with "OGT 918" printed in black on the cap and "100" printed in black on the body.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

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

5.1 Peripheral Neuropathy

In clinical trials, cases of peripheral neuropathy have been reported in 3% of Gaucher's 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 of peripheral neuropathy such as pain, weakness, numbness and tingling should have a careful re-assessment of the risk/benefit of Zavesca therapy, and cessation of treatment may be considered.

5.2 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. Reduce dose to ameliorate tremor or discontinue treatment if tremor does not resolve within days of dose reduction.

5.3 Diarrhea and Weight Loss

Diarrhea and weight loss were common in clinical studies of patients treated with Zavesca, occurring in approximately 85% and up to 65% of treated patients, respectively. Diarrhea appears to be the result of the inhibitory activity of Zavesca on intestinal disaccharidases such as sucrase-isomaltase in the gastrointestinal tract leading to reduced absorption of dietary disaccharides in the small intestine, 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. Diarrhea decreased over time with continued Zavesca treatment, and may respond to individualized diet modification (e.g.,

reduction of sucrose, lactose and other carbohydrate intake), to taking Zavesca between meals, and/or to 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.

5.4 Reductions in Platelet Count

In clinical trials evaluating the use of Zavesca for treatment of indications other than type 1 Gaucher disease, 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 150×10^9/L) before starting treatment with Zavesca. Monitoring of platelet counts is recommended in patients with type 1 Gaucher disease. Mild reductions in platelet counts without association with bleeding were observed in patients with type 1 Gaucher disease who were switched from enzyme replacement therapy (ERT) to Zavesca.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in the labeling:

- Peripheral Neuropathy *[see Warnings and Precautions (5.1)]*
- Tremor *[see Warnings and Precautions (5.2)]*
- Diarrhea and weight loss *[see Warnings and Precautions (5.3)]*
- Reductions in platelet count *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

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.

The data described below reflect exposure of 80 patients with type 1 Gaucher disease in two open-label, uncontrolled, monotherapy trials, one open-label, active-controlled trial, and two extensions, who received Zavesca at doses ranging from 50mg to 200 mg three times daily. Patients were aged 18 to 69 years at first treatment. The population was evenly distributed by gender.

The most common serious adverse reaction reported with Zavesca treatment in clinical trials was peripheral neuropathy *[see Warnings and Precautions (5.1)]*.

The most commonly reported adverse reactions in patients treated with Zavesca (occuring in ≥5%) that were considered related to Zavesca are shown in Tables 1 and 2. *[see Warnings and Precautions (5.2 ,5.3)]*.

The most common adverse reactions requiring intervention were diarrhea and tremor. *[see Warnings and Precautions (5.2, 5.3)]*.

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 1 below lists adverse reactions that occurred during the trials in ≥5% of patients.

Table 1: Adverse Reactions in ≥5% of Patients in Two Open-Label, Uncontrolled

Monotherapy Trials of Zavesca

	Incidence of adverse reactions	
	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
Leg cramps	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, 36 adult type 1 Gaucher disease patients were treated with Zavesca, imiglucerase, or Zavesca plus imiglucerase [Study 3] for up to 12 months. Table 2 lists adverse reactions that occurred during the trial in ≥5% of patients.

Table 2: Adverse Reactions in ≥5% of Patients in Open-Label Active Controlled Study

	Incidence of adverse reactions

	Zavesca alone	Imiglucerase alone
Patients entered in Study (n)	12	12
Body System - Preferred Term	% of patients reporting	% of patients reporting
Gastrointestinal System		
Diarrhea	100	0
Abdominal Pain	67	0
Flatulence	50	0
Constipation	8	0
Nausea	8	0
Dry Mouth	8	0
Body as a Whole		
Pain	0	8
Generalized weakness	17	0
Abdominal distension	8	0
Back pain	8	0
Heaviness in limbs	8	0
Metabolic and Nutritional Disorders		
Weight Decrease	67	0
Central and Peripheral Nervous System		
Tremor	17	0
Dizziness	8	0
Leg cramps	8	0
Unsteady gait	8	0
Psychiatric disorders		
Memory loss	8	0

7 DRUG INTERACTIONS

While co-administration of Zavesca appeared to increase the clearance of imiglucerase by 70%, these results are not conclusive because of the small number of patients studied and because patients took variable doses of imiglucerase *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well controlled studies with Zavesca in pregnant women. However, animal reproduction studies have been conducted for Zavesca. In these animal studies, decreased live births and decreased fetal weight were observed in rats orally dosed with miglustat prior to mating and during organogenesis at doses with exposures at and greater than 2 times the human therapeutic systemic exposure. Maternal death and decreased body weight gain were observed in rabbits orally dosed with miglustat during organogenesis at doses with exposures less than the human therapeutic systemic exposure. Zavesca should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Disease-associated maternal and embryo-fetal risk

Women with Type 1 Gaucher disease have an increased risk of spontaneous abortion, especially if disease symptoms are not treated and controlled pre-conception and during a pregnancy. Pregnancy may exacerbate existing Type 1 Gaucher disease symptoms or result in new disease manifestations. Type 1 Gaucher disease manifestations may lead to adverse pregnancy outcomes including, hepatosplenomegaly which can interfere with the normal growth of a pregnancy and thrombocytopenia which can lead to increased bleeding and possible hemorrhage.

Labor or delivery

Dystocia and delayed parturition were observed in rats dosed with miglustat gestation day 6 through lactation at systemic exposure ≥2 times the human therapeutic systemic exposure.

Data

Animal Data

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 were observed in the mid-dose 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 exposure ≥2 times the human therapeutic systemic exposure, based on body surface 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).

A pre and postnatal development study in rats showed no evidence of any adverse effect on pre and postnatal development at oral doses up to 180 mg/kg/day (about 6 times the recommended daily human dose of 5 mg/kg based on body surface area).

8.3 Nursing Mothers

It is not known whether miglustat is present 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, 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.

8.4 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.

8.5 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.

8.6 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 *[see Clinical Pharmacology (12.3)]*.

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 100 mg once a day.

Use of Zavesca in patients with severe renal impairment (creatinine clearance < 30 mL/min/1.73 m^2) 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. The impact of hemodialysis on the disposition of Zavesca has not been investigated.

8.7 Females and Males of Reproductive Potential

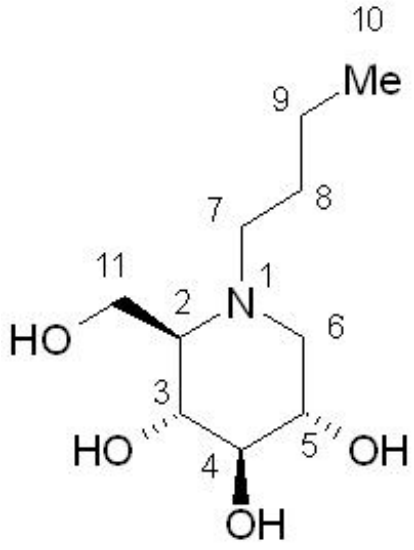
Infertility

No effect on sperm concentration, motility, or morphology was seen in 7 healthy adult men who received miglustat 100 mg, orally, twice daily for 6 weeks. Decreased spermatogenesis with altered sperm morphology and motility and decreased fertility were observed in rats orally dosed with miglustat 14 days prior to mating with doses at exposures less than the human therapeutic systemic exposure based on body surface area comparisons (mg/m^2). Decreased spermatogenesis was reversible in rats following 6 weeks of drug withdrawal [*see Nonclinical Toxicology (13.1)*].

11 DESCRIPTION

Zavesca (miglustat capsules, 100 mg) 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 (>1000 mg/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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Type 1 Gaucher disease is caused by a functional deficiency of glucocerebrosidase, the enzyme that mediates the degradation of the glycosphingolipid glucosylceramide.

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.

Zavesca helps 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.

12.3 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 three times daily in Gaucher patients, exhibits dose-proportional pharmacokinetics. The pharmacokinetics of miglustat were not altered after repeated dosing three times daily for up to 12 months.

In healthy subjects, co-administration of Zavesca with food results in a decrease in the rate of absorption of miglustat (maximum plasma concentration [C_{max}] was decreased by 36% and t_{max} delayed 2 h) but had no statistically significant effect on the extent of absorption of miglustat (area-under-the-plasma-concentration time 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. The pharmacokinetics of miglustat were similar between adult type 1 Gaucher disease patients and healthy subjects after a single dose administration of miglustat 100 mg.

Distribution: Miglustat does not bind to plasma proteins. Mean apparent volume of distribution of miglustat is 83-105 liters in Gaucher patients. At steady state, the concentration of miglustat in cerebrospinal fluid of six non-Gaucher patients was 31.4-67.2% of that in plasma, indicating that miglustat crosses the blood brain barrier.

Metabolism and Excretion: The major route of excretion of miglustat is via kidney. Following administration of a single dose of 100 mg ^{14}C-miglustat to healthy volunteers, 83% of the radioactivity was recovered in urine and 12% in feces. In healthy subjects, 67% of the administered dose was excreted unchanged in urine over 72 hours. The most abundant metabolite in urine was miglustat glucuronide accounting for 5% of the dose. The terminal half-life of radioactivity in plasma was 150 hours, suggesting the presence of one or more metabolites with a prolonged half-life. The metabolite accounting for this observation has not been identified, but may accumulate and reach concentrations exceeding those of miglustat at steady state.

Specific 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 Impairment: No studies have been performed to assess the pharmacokinetics of miglustat in patients with hepatic impairment.

Renal Impairment: Limited data in non-Gaucher patients with impaired renal function indicate that the apparent oral 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 the apparent oral clearance 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 (2.2)]*.

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 *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)]*.

Drug Interaction Studies

Miglustat does not inhibit the metabolism of various substrates of cytochrome P450 enzymes including, CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP4A11 *in vitro*; consequently significant interactions via inhibition of these enzymes are unlikely with drugs that are substrates of cytochrome P450 enzymes.

Drug interaction between Zavesca (miglustat 100 mg orally three times daily) and imiglucerase 7.5 or 15 U/kg/day was assessed in imiglucerase-stabilized 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 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 imiglucerase *[see Drug Interactions (7)]*.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: 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, 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).

Mutagenesis: 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.

Impairment of Fertility: 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.

13.2 Animal Toxicology and/or Pharmacology

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.

14 CLINICAL STUDIES

The efficacy of Zavesca in type 1 Gaucher disease has been investigated in two open-label, uncontrolled trials and one randomized, open-label, active-controlled trial with enzyme replacement given as imiglucerase. 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 trials and their extension period.

Open-Label Uncontrolled Monotherapy Trials

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 to 200 mg three times daily) to 28 adult patients with type 1 Gaucher disease,

who were unable to receive enzyme replacement therapy and who had not taken enzyme replacement therapy in the preceding 6 months. Twenty-two patients completed the trial. 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 8×10^9/L (See Tables 3-6).

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 to receive enzyme replacement therapy and who had not taken enzyme replacement therapy in the preceding 6 months. Seventeen patients completed the trial. 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 5×10^9/L (See Tables 3-6).

Extension Period

Eighteen patients were enrolled in a 12-month extension to Study 1. A subset of patients continuing in the extension had larger mean baseline liver volumes, and lower mean baseline platelet counts and hemoglobin concentrations than the original study population (See Tables 3-6). After a total of 24 months of treatment, there were significant mean decreases from baseline in liver and spleen organ volumes of 15% and 27%, respectively, and significant mean absolute increases from baseline in hemoglobin concentration and platelet count of 0.9 g/dL and 14×10^9/L, respectively (See Tables 3-6).

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 3-6).

Liver volume results from Studies 1 and 2 and their extensions are summarized in Table 3:

Table 3: Liver Volume Changes in Two Open-Label Uncontrolled Monotherapy Trials of Zavesca with Extension Period

		Liver Volume	
	n	**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 4:

Table 4: Spleen Volume Changes in Two Open-Label Uncontrolled Monotherapy Trials of Zavesca with Extension Period

	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 5:

Table 5: Hemoglobin Concentration Changes in Two Open-Label Uncontrolled Monotherapy Trials of Zavesca with Extension Period

	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)

Platelet count results from Studies 1 and 2 and their extensions are summarized in Table 6:

Table 6: Platelet Count Changes in Two Open-Label Uncontrolled Monotherapy Trials of Zavesca with Extension Period

	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 Trial

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 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:

- Zavesca 100 mg three times daily alone
- imiglucerase (patient's usual dose) alone
- Zavesca 100 mg three times daily and imiglucerase (usual dose)

Patients were treated for 6 months, and 33 patients completed the study. Because Zavesca is only indicated as monotherapy, the results for the monotherapy arms are described below. At Month 6, the results showed a decrease in mean percent change in liver volume in the Zavesca treatment group compared to the imiglucerase 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 imiglucerase alone groups in platelet counts at Month 6, with the Zavesca alone group having a mean absolute decrease in platelet count of 21.6 × 10^9/L and the imiglucerase alone group having a mean absolute increase in platelet count of 10.1 × 10^9/L (See Tables 7-10).

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 imiglucerase 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 the treatment groups (by original randomization). There was a significant decrease in platelet counts from Month 6 to Month 12 in the group originally randomized to treatment with imiglucerase, 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 7-10).

Liver volume results from Study 3 and extension are summarized in Table 7:

Table 7: Liver Volume Changes from Study 3 and Extension Phase

	Imiglucerase alone	Zavesca alone

Study 3	n=11	n=10
Month 0	1.81	1.58
Month 6 Change (L)	0.04	-0.05
Month 6 % Change	3.6%	-2.9%
Adjusted mean Difference from Imiglucerase (95% CI)		-4.5% (-13.2, 4.2)
Extension Phase*	n=10	n=8
Month 0	1.94	1.60
Month 12 Change (L)	-0.05	-0.01
Month 12 % Change	-0.7%	-0.8%

* 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 8:

Table 8: Spleen Volume Changes from Study 3 and Extension Phase

	Imiglucerase alone	**Zavesca alone**
Study 3	n=8	n=7
Month 0	0.61	0.69
Month 6 Change (L)	-0.02	-0.03
Month 6 % Change	-2.1%	-4.8%
Adjusted % Difference from Imiglucerase (95% CI)		-5.8% (-22.1, 10.5)
Extension Phase*	n=7	n=6
Month 0	0.83	0.57
Month 12 Change (L)	0.04	-0.05
Month 12 % Change	1.5%	-6.1%

* 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 9:

Table 9: Hemoglobin Concentration Changes from Study 3 and Extension Phase

	Imiglucerase alone	**Zavesca alone**
Study 3	n=12	n=10
Month 0	13.18	12.44
Month 6 Change (g/dL)	-0.15	-0.31
Month 6 % Change	-1.2%	-2.4%
Adjusted % Difference from Imiglucerase (95% CI)		-1.9% (-6.4, 2.6)
Extension Phase*	n=10	n=9
Month 0	13.39	12.46
Month 12 Change (g/dL)	-0.48	-0.13
Month 12 % Change	-3.1%	-1.1%

* 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 10:

Table 10: Platelet Count Changes from Study 3 and Extension Phase

	Imiglucerase alone	Zavesca alone
Study 3	n=12	n=10
Month 0	165.75	170.55
Month 6 Change (10^9/L)	15.29	-21.60
Month 6 % Change	10.1%	-9.6%
Adjusted % Difference from Imiglucerase (95% CI)		-17.1% (-32.9, -1.3)
Extension Phase*	n=10	n=9
Month 0	170.05	184.83
Month 12 Change (10^9/L)	-3.75	-27.39
Month 12 % Change	-3.2%	-10.4%

* All patients received Zavesca 100 mg three times daily monotherapy from Month 6 to Month 12.

Patients with platelet counts above 150 × 10^9/L at baseline who were randomized to Zavesca treatment had significant decreases in platelet counts at Month 12.

16 HOW SUPPLIED/STORAGE AND HANDLING

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. Six blister cards of 15 capsules are supplied in each carton.

NDC 66215-201-90: carton containing 90 capsules.
NDC 66215-201-15: blister card containing 15 capsules

Storage: Store at 20°C to 25°C (68° to 77°F). Brief exposure to 15°C to 30°C (59°F to 86°F) permitted (see USP Controlled Room Temperature).

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

Information for Patients

- Advise patients that the most common serious adverse reactions reported with Zavesca are peripheral neuropathy. Advise patients to promptly report any numbness, tingling, pain, or burning in the hands and feet *[see Warnings and Precautions (5.1)]*.
- Advise patients that other adverse reactions include tremor and reductions in platelet counts. Advise patients to promptly report the development of tremor or worsening in an existing tremor. *[see Warnings and Precautions (5.2 and 5.4)]*
- Advise patients that other serious adverse reactions include diarrhea and weight loss. Advise patients to adhere to dietary instructions *[see Warnings and Precautions (5.3)]*.
- Advise patients to take the next Zavesca capsule at the next scheduled time if a dose is missed.
- Inform patients of the potential risks and benefits of Zavesca and of alternative modes of therapy.

Manufactured for:
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Patient Information
ZAVESCA® (zah-VEHS-kah)
(miglustat)
Capsules

Read this Patient Information before you start taking Zavesca and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

What is Zavesca?

Zavesca is a prescription medicine used alone to treat 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.

What should I tell my doctor before taking Zavesca?

Before you take Zavesca tell your doctor if you:
- have kidney problems
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if Zavesca will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if Zavesca passes into your breast milk. You and your doctor should decide if you will breastfeed or take Zavesca. You should not do both.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Zavesca may affect how other medicines work.

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

How should I take Zavesca?
- Take Zavesca exactly as your doctor has prescribed.
- Take Zavesca at the same time each day.
- If you miss a dose of ZAVESCA, skip that dose. Take the next ZAVESCA capsule at the usual time.

What are the possible side effects of Zavesca?

Zavesca may cause serious side effects including:
- **Numbness, tingling, pain, or burning in your hands or feet (peripheral neuropathy).** Call your doctor right away if you get numbness, tingling, pain, or burning in your hands or feet.
- Your doctor may test your nerves (neurological exam) before you start Zavesca and during treatment with Zavesca.
- **New or worsening hand tremors (shaky movements).** Tremors are common with Zavesca and may begin within the first month of starting treatment. Sometimes the tremors may go away between 1 to 3 months with continued treatment. Your doctor may lower your dose or stop Zavesca if you develop new or worsening hand tremors. Call your doctor right away if you get new hand tremors while taking Zavesca or if the hand tremors you already have get worse.
- **Diarrhea** is common with Zavesca and sometimes can be serious. Your doctor may prescribe another medicine (anti-diarrheal) to treat diarrhea if it is a problem for you and may recommend

changes to your diet, such as avoiding foods high in carbohydrates. Talk with your doctor about your diet if you have diarrhea.

- **Weight loss** is common with Zavesca and sometimes can be serious. You may lose weight when you start treatment with Zavesca.
- **Low platelet count** is common with Zavesca and can be serious. Your doctor may do blood tests to monitor your blood platelet count.

The most common side effects of Zavesca are:

- Weight loss
- Stomach pain
- Gas
- Nausea and vomiting
- Headache, including migraine
- Leg cramps
- Dizziness
- Weakness
- Vision problems
- Muscle cramps
- Back pain
- Constipation
- Dry mouth
- Heaviness in arms and legs
- Memory loss
- Unsteady walking
- Loss of appetite
- Indigestion
- Numbness, tingling, pain, or burning of your skin
- Stomach bloating
- Stomach pain not related to food
- Menstrual changes

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Zavesca. For more information, ask your doctor or pharmacist.

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

How should I store Zavesca?

- Store Zavesca at room temperature between 68°F to 77°F (20°C to 25°C).

Keep Zavesca and all medicines out of the reach of children.

General information about the safe and effective use of Zavesca.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. 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.

If you would like more information, talk with your doctor. You can ask your 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.

The capsule shell contains: gelatin and titanium dioxide; the edible printing ink contains black iron oxide and shellac.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured for:

Actelion Pharmaceuticals US Inc
5000 Shoreline Court, Ste 200
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(650) 624 6900
Revised: 07/2015

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ACT20150722

PRINCIPAL DISPLAY PANEL - 90 Capsule Carton

NDC 66215-201-90
Rx Only

zavesca® 100 mg
(miglustat) capsules

90 capsules
Oral use

ACTELION

ZAVESCA

miglustat capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:66215-201
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength

miglustat (UNII: ADN3S497AZ) (miglustat - UNII:ADN3S497AZ)	miglustat	100 mg

Inactive Ingredients

Ingredient Name	Strength
sodium starch glycolate type a potato (UNII: 5856J3G2A2)	
povidone k30 (UNII: U725QWY32X)	
magnesium stearate (UNII: 70097M6I30)	
gelatin (UNII: 2G86QN327L)	
titanium dioxide (UNII: 15FIX9V2JP)	
ferrosoferric oxide (UNII: XM0M87F357)	
shellac (UNII: 46N107B71O)	

Product Characteristics

Color	WHITE (white opaque)	**Score**	no score
Shape	CAPSULE	**Size**	14mm
Flavor		**Imprint Code**	OGT;918;100
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:66215-201-90	6 in 1 CARTON		
1	NDC:66215-201-15	15 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021348	07/31/2003	

Labeler - Actelion Pharmaceuticals US, Inc. (002641228)

Revised: 2/2016 Actelion Pharmaceuticals US, Inc.