miglustat capsules, for oral use

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use miglustat safely and
effectively. See full prescribing information for miglustat.
miglustat capsules, for oral use
Initial U.S. Approval: 2003

INDICATIONS AND USAGE
Miglustat 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).
• Adjust in patients with renal impairment (2.2):

<table>
<thead>
<tr>
<th>Renal Impairment</th>
<th>Adjusted Creatinine Clearance (in mL/min/1.73 m²)</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>50 – 70</td>
<td>Start dose at 100 mg twice a day</td>
</tr>
<tr>
<td>Moderate</td>
<td>30 – 50</td>
<td>Start dose at 100 mg once a day</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;30</td>
<td>Use is not recommended</td>
</tr>
</tbody>
</table>

Dosage Forms and Strengths
Capsules: 100 mg (3)

CONTRAINDICATIONS
None (4)

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8.1 Pregnancy
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8.3 Females and Males of Reproductive Potential
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10 NONCLINICAL TOXICOLOGY

11 DESCRIPTION

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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 m²), initiate miglustat treatment at a dose of 100 mg twice per
day. In patients with moderate renal impairment (adjusted creatinine clearance 30-50 mL/min/1.73 m²), initiate miglustat treatment at a dose of one 100 mg capsule per
day. Miglustat is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m²) [see Use in Specific Populations (8.6)].

3 DOSAGE FORMS AND STRENGTHS
Capsules: 100 mg of miglustat, 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

5.1 Peripheral Neuropathy
In clinical trials, cases of peripheral neuropathy have been reported in 3% of Gaucher’s patients treated with miglustat. All patients receiving miglustat 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 miglustat 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 miglustat, occurring in approximately 85% and up to 65% of treated patients, respectively. Diarrhea appears to be the result of the inhibitory activity of miglustat 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 miglustat treatment, and may respond to individualized diet modification (e.g., reduction of sucrose, lactose and other carbohydrate intake), to taking miglustat between meals, and/or to anti-diarrheal medications, most commonly loperamide. Patients may be instructed to avoid high carbohydrate content foods during treatment with miglustat if they present with diarrhea.

Patients with persistent gastrointestinal events that continue during treatment with miglustat, 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 miglustat has not been evaluated in patients with significant gastrointestinal disease, such as inflammatory bowel disease, and continued treatment of these patients with miglustat 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 miglustat 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 150×10⁹/L) before starting treatment with miglustat. 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 miglustat.

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 miglustat at doses ranging from 50 mg 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 commonly reported adverse reactions in patients treated with miglustat in clinical trials was peripheral neuropathy [see Warnings and Precautions (5.1)].

In an open-label, active-controlled study, 36 adult type 1 Gaucher disease patients were treated with miglustat, imiglucerase, or miglustat plus imiglucerase [Study 3] for up to 12 months. Table 2 lists adverse reactions that occurred during the trial in ≥5% of patients.

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

<table>
<thead>
<tr>
<th>Incidence of adverse reactions</th>
<th>Study 1 (starting dose 100 mg three times daily)</th>
<th>Study 2 (50 mg three times daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients entered in Study (n)</td>
<td>28</td>
<td>18</td>
</tr>
<tr>
<td>Body System - Preferred Term</td>
<td>% of patients reporting</td>
<td>% of patients reporting</td>
</tr>
<tr>
<td>Gastrointestinal System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>Flatulence</td>
<td>29</td>
<td>44</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>18</td>
<td>50</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Bloating</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Anorexia</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Epigastric pain not food-related</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Metabolic and Nutritional Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Decrease</td>
<td>39</td>
<td>67</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Incidence of adverse reactions</th>
<th>Miglustat alone</th>
<th>Imiglucerase alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients entered in Study (n)</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Body System - Preferred Term</td>
<td>% of patients reporting</td>
<td>% of patients reporting</td>
</tr>
<tr>
<td>Gastrointestinal System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>67</td>
<td>0</td>
</tr>
<tr>
<td>Flatulence</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>8</td>
<td>0</td>
</tr>
</tbody>
</table>
Miglustat was also administered to pregnant rats at dose levels 6 times the recommended human dose on a mg/m² basis. There was no effect on behavioral and learning assessments, sexual maturation or reproductive performance of the offspring at doses up to 180 mg/kg/day (about 6 times the human therapeutic dose on a mg/m² basis).

8.2 Lactation

Risk Summary

There are no available data on the ingestion of miglustat by nursing mothers. Milk, the effects on the breastfed infant, or the effects on milk production. Based on the physical properties of miglustat, it is likely to be present in breast milk. Due to the potential for serious adverse reactions in breastfed infants, advise women that breastfeeding is not recommended.

8.3 Females and Males of Reproductive Potential

Infertility

Findings from a small clinical study in four healthy adult males who received miglustat for six weeks did not indicate effects on male fertility. Studies in male rats have shown that miglustat decreased fertility but findings were reversible. Studies in female rats have shown increased post-implantation loss and decreased embryo-fetal survival [see Use in Specific Populations (8.1), Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

The safety and effectiveness of miglustat 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 miglustat 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 miglustat on long-term gain in weight and height in pediatric patients is unclear.

8.5 Geriatric Use

Clinical studies of miglustat 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 based on age and of concomitant disease or other drug therapy.

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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 (administered in the setting of a creatinine clearance of 30-50 mL/min/1.73 m²), miglustat administration should commence at a dose of 100 mg twice per day.

In patients with moderate renal impairment (administered in the setting of a creatinine clearance <30 mL/min/1.73 m²), miglustat administration should commence at a dose of 100 mg once a day.

Use of miglustat in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m²) 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 miglustat has not been investigated.

11 DESCRIPTION

Miglustat (miglustat capsules, 100 mg) is a glucosylceramide synthase inhibitor, which is a glucosyl transferase enzyme responsible for the first step in the synthesis of glucosylceramide, a major component of the lysosomal storage disease Gaucher disease. Miglustat inhibits the enzyme glucosylceramide synthase, which catalyzes the synthesis of glucosylceramide from glucosylceramide and ceramide. This inhibition leads to the accumulation of glucosylceramide in the lysosomes of affected cells, resulting in cytotoxic effects and the development of symptoms associated with Gaucher disease.

12 CLINICAL PHARMACOLOGY

12.1 Pharmacodynamics

Miglustat is a glucosylceramide synthase inhibitor, which inhibits the metabolism of ceramide to glucosylceramide in the synthesis of gangliosides in the plasma membrane of monocytes, causing the accumulation of glucosylceramide and ceramide in the lysosomes of affected cells. This accumulation leads to the cytotoxic effects of glucosylceramide and ceramide, resulting in the development of symptoms associated with Gaucher disease.

12.2 Pharmacokinetics

Following oral administration, miglustat is rapidly absorbed and reaches peak plasma concentrations within 2-4 hours. The absolute bioavailability of miglustat is approximately 70%. Miglustat is extensively metabolized in the liver and is excreted primarily in the urine as inactive metabolites. The half-life of miglustat is approximately 4-6 hours.

12.3 Effect of Renal Impairment

Patients with mild renal impairment (administered in the setting of a creatinine clearance of 30-50 mL/min/1.73 m²), miglustat administration should commence at a dose of 100 mg twice per day.

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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 miglustat has not been investigated.
12 Absorption

Absorption

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.

12.3 Pharmacokinetics

Distribution

Miglustat capsules, for oral use

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 miglustat (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 CL/F and a 14% reduction in the AUC for miglustat. While miglustat 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 1, 2 and 5 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).

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

Miglustat was administered by oral gavage to male rats at doses of 20, 60, 180 mg/kg/day beginning at least 14 days prior to mating and continuing through mating. Effects on sperm parameters (concentration, motility and morphology) resulting in decreased fertility were observed at all dose levels (the lowest dose level was 0.65 times the human therapeutic dose on a mg/m² basis). Reversibility was demonstrated following 6 weeks of drug withdrawal. Findings of, seminiferous tubule degeneration and atrophy were observed in the testes in rat repeat-dose fertility studies.

Miglustat was administered by oral gavage to female rats at doses of 20, 60, 180 mg/kg/day beginning 14 days before mating and continuing through gestation day 17. There were no effects on mating performance or fertility in female rats.
at doses up to 180 mg/kg/day. However, increased post implantation loss and decreased embryo-fetal survival were observed at doses ≥60 mg/kg/day (≥2 times the human therapeutic dose on a mg/m² basis).

### 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/week (6 times the human therapeutic exposure based on body surface area comparisons, mg/m²) 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/m²) 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/m²), 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 1880 mg/kg/d.

Gastrointestinal necrosis, inflammation, and hemorrhage were observed in dogs at ≥85 mg/kg/day (6 times the human therapeutic systemic exposure based on body surface area comparisons, mg/m²) 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 miglustat 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 miglustat 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 miglustat during the three trials and their extension period.

#### Open-Label Uncontrolled Monotherapy Trials

In Study 1, miglustat 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 8×10⁹/L (See Tables 3-6).

In Study 2, miglustat was administered at a dose of 50 mg three times daily for 6 months to 18 adult patients with type 1 Gaucher disease who were unable 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 5×10⁹/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 14×10⁹/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>
<thead>
<tr>
<th>Study</th>
<th>Starting Dose</th>
<th>Liver Volume</th>
<th>n</th>
<th>Absolute Mean (L)</th>
<th>Percent Mean (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(starting dose miglustat 100 mg three times daily)</td>
<td></td>
<td></td>
<td>(2-sided 95% CI)</td>
<td>(2-sided 95% CI)</td>
</tr>
<tr>
<td>Study 1</td>
<td>Baseline (Month 0)</td>
<td>21</td>
<td>2.39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 1</td>
<td>Month 12 Change from baseline</td>
<td></td>
<td>-0.28 (-0.38, -0.18)</td>
<td>-12.1% (-16.4, 7.9)</td>
<td></td>
</tr>
<tr>
<td>Study 1 Extension Phase</td>
<td>Baseline (Month 0)</td>
<td>12</td>
<td>2.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 1 Extension Phase</td>
<td>Month 24 Change from baseline</td>
<td></td>
<td>-0.36 (-0.48, -0.24)</td>
<td>-14.5% (-19.3, 9.7)</td>
<td></td>
</tr>
<tr>
<td>Study 2</td>
<td>Baseline (Month 0)</td>
<td>17</td>
<td>2.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 2</td>
<td>Month 6 Change from baseline</td>
<td></td>
<td>-0.14 (-0.25, -0.03)</td>
<td>-5.9% (-9.9, -1.9)</td>
<td></td>
</tr>
<tr>
<td>Study 2 Extension Phase</td>
<td>Baseline (Month 0)</td>
<td>13</td>
<td>2.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 2 Extension Phase</td>
<td>Month 12 Change from baseline</td>
<td></td>
<td>-0.17 (-0.3, -0.0)</td>
<td>-6.2% (-12.0, -0.5)</td>
<td></td>
</tr>
</tbody>
</table>

Spleen volume results from Studies 1 and 2 and their extensions are summarized in Table 4:

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

Hemoglobin concentration results from Studies 1 and 2 and their extensions are summarized in Table 5:

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

<table>
<thead>
<tr>
<th></th>
<th>miglustat alone</th>
<th>Imiglucerase alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute Mean (10^9/L)</td>
<td>n</td>
<td>(2-sided 95% CI)</td>
</tr>
<tr>
<td>Baseline (Month 0)</td>
<td>76.58</td>
<td></td>
</tr>
<tr>
<td>Month 12 Change from baseline</td>
<td>72.35</td>
<td></td>
</tr>
</tbody>
</table>

#### Study 1 Extension Phase

<table>
<thead>
<tr>
<th></th>
<th>miglustat alone</th>
<th>Imiglucerase alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (Month 0)</td>
<td>116.47</td>
<td></td>
</tr>
<tr>
<td>Month 6 Change from baseline</td>
<td>5.35 (-6.31, 17.02)</td>
<td>2.0% (-6.9, 10.8)</td>
</tr>
</tbody>
</table>

#### Study 2 Extension Phase

<table>
<thead>
<tr>
<th></th>
<th>miglustat alone</th>
<th>Imiglucerase alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (Month 0)</td>
<td>122.15</td>
<td></td>
</tr>
<tr>
<td>Month 12 Change from baseline</td>
<td>14.0 (-3.4, 31.4)</td>
<td>14.7% (-1.4, 30.7)</td>
</tr>
</tbody>
</table>

#### Open-Label Active-Controlled Trial

- miglustat 100 mg three times daily
- imiglucerase (patient’s usual dose) alone
- miglustat 100 mg three times daily and imiglucerase (usual dose)

Patients were treated for 6 months, and 33 patients completed the study. Because miglustat 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 miglustat 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 miglustat alone and imiglucerase alone groups in platelet counts at Month 6, with the miglustat alone group having a mean absolute decrease in platelet count of 21.6×10^9/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 miglustat 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 miglustat 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

<table>
<thead>
<tr>
<th></th>
<th>miglustat alone</th>
<th>Imiglucerase alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 3</td>
<td>n=11</td>
<td>n=10</td>
</tr>
<tr>
<td>Month 0</td>
<td>1.81</td>
<td>1.58</td>
</tr>
<tr>
<td>Month 6 Change (L)</td>
<td>0.04</td>
<td>-0.05</td>
</tr>
<tr>
<td>Month 6 % Change</td>
<td>3.6%</td>
<td>-2.9%</td>
</tr>
<tr>
<td>Adjusted mean Difference from Imiglucerase (95% CI)</td>
<td>-4.5% (-13.2, 4.2)</td>
<td></td>
</tr>
</tbody>
</table>

**Extension Phase**

<table>
<thead>
<tr>
<th></th>
<th>miglustat alone</th>
<th>Imiglucerase alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 0</td>
<td>1.94</td>
<td>1.60</td>
</tr>
<tr>
<td>Month 12 Change (L)</td>
<td>-0.05</td>
<td>-0.01</td>
</tr>
<tr>
<td>Month 12 % Change</td>
<td>-0.7%</td>
<td>-0.8%</td>
</tr>
</tbody>
</table>

* All patients received miglustat 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

<table>
<thead>
<tr>
<th></th>
<th>Imiglucerase alone</th>
<th>miglustat alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 3</td>
<td>n=8</td>
<td>n=7</td>
</tr>
<tr>
<td>Month 0</td>
<td>0.61</td>
<td>0.69</td>
</tr>
<tr>
<td>Month 6 Change (L)</td>
<td>-0.02</td>
<td>-0.03</td>
</tr>
<tr>
<td>Month 6 % Change</td>
<td>-2.1%</td>
<td>-4.8%</td>
</tr>
<tr>
<td>Adjusted % Difference from Imiglucerase (95% CI)</td>
<td>-5.8% (-22.1, 10.5)</td>
<td></td>
</tr>
</tbody>
</table>

**Extension Phase**

<table>
<thead>
<tr>
<th></th>
<th>Imiglucerase alone</th>
<th>miglustat alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 0</td>
<td>0.83</td>
<td>0.57</td>
</tr>
<tr>
<td>Month 12 Change (L)</td>
<td>0.04</td>
<td>-0.05</td>
</tr>
<tr>
<td>Month 12 % Change</td>
<td>1.5%</td>
<td>-6.1%</td>
</tr>
</tbody>
</table>

* All patients received miglustat 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

<table>
<thead>
<tr>
<th></th>
<th>Imiglucerase alone</th>
<th>miglustat alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 3</td>
<td>n=12</td>
<td>n=10</td>
</tr>
<tr>
<td>Month 0</td>
<td>13.18</td>
<td>12.44</td>
</tr>
<tr>
<td>Month 6 Change (g/dL)</td>
<td>-0.15</td>
<td>-0.31</td>
</tr>
<tr>
<td>Month 6 % Change</td>
<td>-1.2%</td>
<td>-2.4%</td>
</tr>
<tr>
<td>Adjusted % Difference from Imiglucerase (95% CI)</td>
<td>-1.9% (-6.4, 2.6)</td>
<td></td>
</tr>
</tbody>
</table>

**Extension Phase**

<table>
<thead>
<tr>
<th></th>
<th>Imiglucerase alone</th>
<th>miglustat alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 0</td>
<td>13.39</td>
<td>12.46</td>
</tr>
<tr>
<td>Month 12 Change (g/dL)</td>
<td>-0.48</td>
<td>-0.13</td>
</tr>
<tr>
<td>Month 12 % Change</td>
<td>-3.1%</td>
<td>-1.1%</td>
</tr>
</tbody>
</table>

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

16 HOW SUPPLIED/STORAGE AND HANDLING

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

Miglustat 100 mg capsules are packed in blister cards. Six blister cards of 15 capsules are supplied in each carton.

NDC 10148-201-90: blister card containing 15 capsules
NDC 10148-201-90: carton containing 90 capsules
NDC 10148-201-90: blister card containing 15 capsules

Storage
Store at 20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature].

Keep out of reach of children.
17 PATIENT COUNSELING INFORMATION
Advising the patient to read the FDA-approved patient labeling (Patient Information).

Information for Patients
- Advise patients that the most common serious adverse reaction reported with miglustat is 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, 5.4)].
- Advise patients that other serious adverse reactions include diarrhea and weight loss. Advise patients to promptly report any development of diarrhea or weight loss [see Warnings and Precautions (5.3)].
- Advise patients to take the next miglustat capsule at the next scheduled time if a dose is missed.
- Inform patients of the potential risks and benefits of miglustat and of alternative modes of therapy.

Pregnancy
Advise pregnant women and females of reproductive potential of the potential risk to a fetus, based on animal data. Advise patients who may become pregnant to inform their healthcare provider of a known or suspected pregnancy [see Use in Specific Populations (8.1)].

Lactation
Advise women not to breastfeed if they are taking miglustat [see Use in Specific Populations (8.2)].

Manufactured for:
CoTherix, Inc.
Titusville, NJ 08560, USA

JN20221206
### What is MIGLUSTAT?
Miglustat is a prescription medicine used alone to treat adults with mild to moderate type 1 Gaucher disease. Miglustat is used only in people who cannot be treated with enzyme replacement therapy.

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

### Before taking MIGLUSTAT, tell your healthcare provider about all of your medical conditions, including if you:
- have kidney problems
- are pregnant or plan to become pregnant. Miglustat may harm your unborn baby. Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with miglustat.
- are breastfeeding or plan to breastfeed. It is not known if miglustat can pass into your breast milk and may harm your baby. Do not breastfeed during treatment with miglustat. Talk to your healthcare provider about the best way to feed your baby during treatment with miglustat.

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

### How should I take MIGLUSTAT?
- Take miglustat exactly as your healthcare provider tells you to.
- Take miglustat at the same time each day.
- If you miss a dose of miglustat, skip that dose. Take the next miglustat capsule at the usual time.

### What are the possible side effects of MIGLUSTAT?
Miglustat may cause serious side effects including:
- **Numbness, tingling, pain, or burning in your hands or feet (peripheral neuropathy).** Call your healthcare provider right away if you get numbness, tingling, pain, or burning in your hands or feet.
- Your healthcare provider may test your nerves (neurological exam) before you start miglustat and during treatment with miglustat.
- **New or worsening hand tremors (shaky movements).** Tremors are common with miglustat 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 healthcare provider may lower your dose or stop miglustat if you develop new or worsening hand tremors. Call your healthcare provider right away if you get new hand tremors during treatment with miglustat or if the hand tremors you already have get worse.
- **Diarrhea** is common with miglustat and sometimes can be serious. Your healthcare provider 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 healthcare provider about your diet if you have diarrhea.
- **Weight loss** is common with miglustat and sometimes can be serious. You may lose weight when you start treatment with miglustat.
- **Low platelet count** is common with miglustat and can be serious. Your healthcare provider may do blood tests to monitor your blood platelet count during treatment with miglustat.

The most common side effects of miglustat include:
- weight loss
- stomach pain
- gas
- nausea and vomiting
- headache, including migraine
- back pain
- constipation
- dry mouth
- heaviness in arms and legs
- memory loss
- unsteady walking
- leg cramps
- dizziness
- weakness
- vision problems
- muscle cramps
- loss of appetite
- indigestion
- numbness, tingling, pain, or burning of your skin
- stomach bloating
- stomach pain not related to food
- menstrual changes

These are not all of the possible side effects of miglustat.

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

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

### General information about the safe and effective use of MIGLUSTAT.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use miglustat for a condition for which it was not prescribed. Do not give miglustat to other people, even if they have the same symptoms you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about miglustat that is written for health professionals.

### What are the ingredients in MIGLUSTAT?
**Active ingredient:** miglustat  
**Inactive ingredients:** magnesium stearate, povidone (K30), and sodium starch glycolate.  
**The capsule shell contains:** gelatin and titanium dioxide; the edible printing ink contains black iron oxide and shellac.

**Manufactured for:**  
CoTherix, Inc.  
Titusville, NJ 08560, USA  
JN20221206

This Patient Information has been approved by the U.S. Food and Drug Administration.  
Revised: 12/2022

cp-162644v5