STATEMENT OF MEDICAL NECESSITY

FOR THE TREATMENT OF GAUCHER DISEASE

Patient Name _____ Insurance ID Number _____

Address _____ City _____ State _____ Zip Code _____

Gender _____ Date of Birth _____ Phone Number _____

Method of Diagnosis _____ Date _____

Prescriber's Last Name _____ Prescriber's First Name _____

Name of Institution/Practice Name _____

Address _____ City _____ State _____ Zip Code _____

Tax ID _____ State License _____ NPI _____

Office Phone _____ Office Fax _____

DIAGNOSIS

☐ Gaucher Disease (Lipidosis) ICD-9CM 272.7 ☐ Gaucher Disease ICD-10-CM E75.22*

SPLENECTOMY

☐ No ☐ Yes: Date _____ Circle One: Total or Partial

ORGANOMEGALY

☐ No ☐ Yes: Spleen Size _____ Liver Size _____

HEMATOLOGY

Anemia ☐ Yes: Hemoglobin _____

Thrombocytopenia ☐ Yes: Platelet Count _____

Bleeding Event ☐ Yes

Other_____

_____

CYP2D6 METABOLIZER STATUS

☐ Extensive metabolizers (EM) ☐ Intermediate metabolizers (IM) ☐ Poor metabolizers (PMs)

Additional supporting documentation attached:

☐ Lab Results ☐ Treatment History ☐ Other Clinical Information

CERDELGA™ (eliglustat) CAPSULES TREATMENT PLAN AND DOSING

NDC 58468-0220-1 (56 capsules; 4 packs with 14 capsules each in a carton)

DOSE

☐ 84mg eliglustat twice daily ☐ 84mg eliglustat once daily

Physician Signature _____ Date _____

*Important Note: ICD-10-CM for dates of service starting on 10/01/15

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CERDELGA™ safely and effectively. See full prescribing information for CERDELGA.

CERDELGA™ (eliglustat) capsules, for oral use
Initial U.S. Approval: 2014

INDICATIONS AND USAGE

CERDELGA is a glucosylceramide synthase inhibitor indicated for the long-term treatment of adult patients with Gaucher disease type 1 who are CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test. (1)

Limitations of Use:
- CYP2D6 ultra-rapid metabolizers may not achieve adequate concentrations of CERDELGA to achieve a therapeutic effect (1)
- A specific dosage cannot be recommended for CYP2D6 indeterminate metabolizers (1)

DOSAGE AND ADMINISTRATION

- Select patients using an FDA-cleared test for determining CYP2D6 genotype (2.1)
- CYP2D6 EMs or IMs: 84 mg orally twice daily (2.2)
- CYP2D6 PMs: 84 mg orally once daily (2.2)
- Swallow capsules whole, do not crush, dissolve or open capsules (2.3)
- Avoid eating grapefruit or drinking grapefruit juice (2.3)

DOSAGE FORMS AND STRENGTHS

- 84 mg capsules (3)

CONTRAINDICATIONS

- CYP2D6 EMs and IMs taking a strong or moderate CYP2D6 inhibitor with a strong or moderate CYP3A inhibitor (4, 5.1, 7.1, 12.2)
- CYP2D6 IMs and PMs taking a strong CYP3A inhibitor (4, 5.1, 7.1, 12.2)

WARNINGS AND PRECAUTIONS

- ECG Changes and Potential for Cardiac Arrhythmias: Not recommended in patients with pre-existing cardiac disease, long QT syndrome, and concomitant use of Class IA and Class III antiarrhythmics (5.2)

ADVERSE REACTIONS

The most common adverse reactions (≥10%) are: fatigue, headache, nausea, diarrhea, back pain, pain in extremities, and upper abdominal pain (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genzyme Corporation at 1-800-745-4447 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Eliglustat is a CYP2D6 and CYP3A substrate. Co-administration of CERDELGA with drugs that inhibit CYP2D6 and CYP3A may significantly increase the exposure to eliglustat and result in prolongation of the PR, QTc, and/or QRS cardiac interval, which could result in cardiac arrhythmias. Consider potential drug interactions prior to and during therapy (5.1, 7.1)
- CYP2D6 IMs and PMs taking moderate CYP3A inhibitors: not recommended (7.1)
- CYP2D6 PMs taking weak CYP3A inhibitors: not recommended (7.1)
- CYP2D6 EMs and IMs taking strong or moderate CYP2D6 inhibitors and CYP2D6 EMs taking strong or moderate CYP3A inhibitors: reduce the dosage to 84 mg once daily (2.2, 7.1)
- Eliglustat is an inhibitor of P-gp and CYP2D6. Co-administration with drugs that are substrates for P-gp or CYP2D6 may result in increased concentrations of the other drug (7.2)
- See Full Prescribing Information for a list of clinically significant drug interactions (7.1, 7.2)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Only administer if the potential benefit justifies the potential risk. 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)
- Renal impairment: Not recommended in moderate to severe impairment (8.6)
- Hepatic impairment: Not recommended (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CERDELGA is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1) who are CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test *[see Dosage and Administration (2.1)]*.

Limitations of Use:
- Patients who are CYP2D6 ultra-rapid metabolizers (URMs) may not achieve adequate concentrations of CERDELGA to achieve a therapeutic effect *[see Clinical Studies (14)]*.
- A specific dosage cannot be recommended for those patients whose CYP2D6 genotype cannot be determined (indeterminate metabolizers) *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection
Select patients with Gaucher disease type 1 based on their CYP2D6 metabolizer status. It is recommended patient genotypes be established using an FDA-cleared test for determining CYP2D6 genotype *[see Indications and Usage (1)]*.

2.2 Recommended Adult Dosage
The recommended dosage of CERDELGA is 84 mg twice daily in CYP2D6 EMs and IMs. The recommended dosage in CYP2D6 PMs is 84 mg once daily; appropriate adverse event monitoring is recommended *[see Adverse Reactions (6.1)]*. The predicted exposures with 84 mg once daily in patients who are CYP2D6 PMs are expected to be similar to exposures observed with 84 mg twice daily in CYP2D6 IMs *[see Clinical Pharmacology (12.3)]*.

Some inhibitors of CYP2D6 and CYP3A are contraindicated with CERDELGA depending on the patient's metabolizer status *[see Contraindications (4)]*. Co-administration of CERDELGA with other CYP2D6 and CYP3A inhibitors may require dosage adjustment depending on the patient's CYP2D6 metabolizer status to reduce the risk of potentially significant adverse reactions *[see* Table 3 *and* Table 4 *in Drug Interactions (7.1)]*.

Reduce the dosage of CERDELGA to 84 mg once daily for:
- CYP2D6 EMs and IMs taking strong or moderate CYP2D6 inhibitors
- CYP2D6 EMs taking strong or moderate CYP3A inhibitors

2.3 Important Administration Instructions
- Swallow capsules whole, preferably with water, and do not crush, dissolve, or open the capsules.
- CERDELGA can be taken with or without food.
- Avoid the consumption of grapefruit or grapefruit juice with CERDELGA because grapefruit is a strong CYP3A inhibitor *[see Drug Interactions (7.1)]*.
- If a dose of CERDELGA is missed, take the prescribed dose at the next scheduled time; do not double the next dose.
- For patients currently treated with imiglucerase, velaglucerase alfa, or taliglucerase alfa, CERDELGA may be administered 24 hours after the last dose of the previous enzyme replacement therapy (ERT).

3 DOSAGE FORMS AND STRENGTHS

CERDELGA is supplied as 84 mg hard gelatin capsules, with a pearl blue-green opaque cap and pearl white opaque body imprinted with "GZ02" in black. Each capsule contains 100 mg eliglustat tartrate, which is equivalent to 84 mg of eliglustat.

4 CONTRAINDICATIONS

CERDELGA is contraindicated in the following patients due to the risk of significantly increased eliglustat plasma concentrations which may result in prolongation of the PR, QTc, and/or QRS cardiac intervals that could result in cardiac arrhythmias. See Table 3 and Table 4 for examples of drugs in each of the categories described *[see Drug Interactions (7.1)]*:
- EMs or IMs taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor.
- IMs or PMs taking a strong CYP3A inhibitor.

5 WARNINGS AND PRECAUTIONS

5.1 Drug-Drug Interactions
Eliglustat is a CYP2D6 and CYP3A substrate. Drugs that inhibit CYP2D6 and CYP3A metabolism pathways may significantly increase the exposure to eliglustat and result in prolongation of the PR, QTc, and/or QRS cardiac intervals that could result in cardiac arrhythmias *[see Clinical Pharmacology (12.2)]*. Some drugs that are inhibitors of CYP2D6 and CYP3A are contraindicated with CERDELGA depending on the patient's CYP2D6 metabolizer status *[see Contraindications (4)]*. See Table 3 and Table 4 for other potentially significant drug interactions *[see Drug Interactions (7.1)]*.

5.2 ECG Changes and Potential for Cardiac Arrhythmias
Use of CERDELGA in patients with pre-existing cardiac conditions has not been studied during clinical trials. Because CERDELGA is predicted to cause increases in ECG intervals (PR, QTc, and QRS) at substantially elevated eliglustat plasma concentrations, use of CERDELGA is not recommended in patients with pre-existing cardiac disease (congestive heart failure, recent acute myocardial infarction, bradycardia, heart block, ventricular arrhythmia), long QT syndrome, and in combination with Class IA (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications *[see Clinical Pharmacology (12.2)]*.

6 ADVERSE REACTIONS

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 most common adverse reactions to CERDELGA (occurring in ≥10% of the 126 GD1 patients treated with CERDELGA across Trials 1 and 2) were fatigue, headache, nausea, diarrhea, back pain, pain in extremities, and upper abdominal pain.

The adverse reaction profile of CERDELGA is based on two controlled studies, Trials 1 and 2. Table 1 presents the profile from the 9-month double-blind, randomized, placebo-controlled trial of 40 treatment-naive patients (Trial 1). Patients were between the ages of 16 and 63 on the date of the first dose of study drug, and included 20 males and 20 females.

Table 1: Adverse Reactions Occurring in ≥10% of Treatment-Naïve GD1 Patients and More Frequently than Placebo (Trial 1)

Adverse Reaction	CERDELGA (N=20) Patients n (%)	Placebo (N=20) Patients n (%)
Arthralgia	9 (45)	2 (10)
Headache	8 (40)	6 (30)
Migraine	2 (10)	0 (0)
Flatulence	2 (10)	1 (5)
Nausea	2 (10)	1 (5)
Oropharyngeal pain	2 (10)	1 (5)

Table 2 presents the profile from the 12-month open-label, randomized, imiglucerase-controlled trial of 159 treated patients switching from enzyme replacement therapy (ERT) (Trial 2). Patients were between the ages of 18 and 69 on the date of the first dose of CERDELGA, and included 87 females and 72 males.

Table 2: Adverse Reactions Occurring in ≥5% of GD1 Patients Switching from Enzyme Replacement Therapy to CERDELGA and More Frequently than Imiglucerase (Trial 2)*

Adverse Reaction	CERDELGA (N=106) Patients n (%)	Imiglucerase (N=53) Patients n (%)
Fatigue	15 (14)	1 (2)
Headache	14 (13)	1 (2)
Nausea	13 (12)	0 (0)
Diarrhea	13 (12)	2 (4)
Back pain	13 (12)	3 (6)
Pain in extremity	12 (11)	1 (2)
Upper abdominal pain	11 (10)	0 (0)
Dizziness	9 (8)	0 (0)
Asthenia	9 (8)	0 (0)
Cough	7 (7)	2 (4)
Dyspepsia	7 (7)	1 (2)
Gastroesophageal reflux disease	7 (7)	0 (0)
Constipation	5 (5)	0 (0)
Palpitations	5 (5)	0 (0)
Rash	5 (5)	0 (0)

*Trial 2 was not designed to support comparative claims for CERDELGA for the adverse reactions reported in this table.

In an uncontrolled study, with up to 4 years of treatment, in 26 patients, the types and incidences of adverse reactions were similar to Trials 1 and 2.

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect CERDELGA
Eliglustat is a CYP2D6 and CYP3A substrate.

CYP2D6 and CYP3A Inhibitors

Drugs that inhibit CYP2D6 and CYP3A pathways may significantly increase the exposure to eliglustat and result in prolongation of the PR, QTc, and/or QRS cardiac interval which could result in cardiac arrhythmias:
- Some inhibitors of CYP2D6 and CYP3A are contraindicated with CERDELGA depending on the patient's CYP2D6 metabolizer status *[see Contraindications (4)]*.
- Co-administration of CERDELGA with other CYP2D6 and CYP3A inhibitors may require dosage adjustment depending on the patient's CYP2D6 metabolizer status to reduce the risk of potential significant adverse reactions (see Table 3 and Table 4).

Table 3: Established and Other Potentially Significant Drug Interactions: Alteration in CERDELGA Dosage May Be Recommended Based on Drug Interaction Studies or on Predicted Interaction in EMs and IMs

	Recommended CERDELGA Dosage, by CYP2D6 Metabolizer Status	
CYP450 Inhibitors	**EM**	**IM**
Strong or Moderate CYP2D6 inhibitors concomitantly with Strong or Moderate CYP3A inhibitors	Contraindicated	Contraindicated
Strong CYP2D6 inhibitors e.g., paroxetine	84 mg once daily	84 mg once daily
Moderate CYP2D6 inhibitors e.g., terbinafine	84 mg once daily	84 mg once daily
Strong CYP3A inhibitors e.g., ketoconazole	84 mg once daily	Contraindicated
Moderate CYP3A inhibitors e.g., fluconazole	84 mg once daily	Not recommended

Table 4: Established and Other Potentially Significant Drug Interactions: Alteration in CERDELGA Dosage May Be Recommended Based on Predicted Interaction in PMs

CYP450 Inhibitors	Recommended CERDELGA Dosage for PMs
Strong CYP3A inhibitors e.g., ketoconazole	Contraindicated
Moderate CYP3A inhibitors e.g., fluconazole	Not recommended
Weak CYP3A inhibitors e.g., ranitidine	Not recommended

CYP3A Inducers
Co-administration of CERDELGA with strong CYP3A inducers significantly decreases eliglustat exposure. Use of CERDELGA with strong CYP3A inducers (e.g., rifampin, carbamazepine, phenobarbital, phenytoin, and St. John's Wort) is not recommended in EMs, IMs, and PMs.

7.2 Potential for CERDELGA to Affect Other Drugs
Eliglustat is an inhibitor of P-gp and CYP2D6. Co-administration of CERDELGA with drugs that are substrates for P-gp or CYP2D6 may result in increased concentrations of the concomitant drug as shown in Table 5.

Table 5: Drug Interactions that Result in Increased Concentrations of the Concomitant Drug

Drug Class or Drug Name	Clinical Recommendations
Digoxin (P-gp substrate)	Measure serum digoxin concentrations before initiating CERDELGA. Reduce digoxin dose by 30% and continue monitoring.
Other P-gp substrates (e.g., phenytoin, colchicine, dabigatran etexilate)	Monitor therapeutic drug concentrations, as indicated, or consider reducing the dosage of the concomitant drug and titrate to clinical effect.
CYP2D6 substrates • Metoprolol; • tricyclic antidepressants (e.g., nortriptyline, amitriptyline, imipramine); • phenothiazines (e.g., perphenazine, chloropromazine).	

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary
There are no adequate or well-controlled studies with CERDELGA in pregnant women. However, animal reproduction studies have been conducted for eliglustat. In these animal studies, a spectrum of anomalies at doses 6 times the recommended human dose were observed in orally dosed rats. No fetal harm was observed with oral administration of eliglustat to pregnant rabbits at dose levels 10 times the recommended human dose. CERDELGA 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 Gaucher disease type 1 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 Gaucher disease type 1 symptoms or result in new disease manifestations. Gaucher disease type 1 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.

Animal Data
Reproduction studies have been performed in pregnant rats at oral doses up to 120 mg/kg/day (about 6 times the recommended human dose based on body surface area) and in pregnant rabbits at oral doses up to 100 mg/kg/day (about 10 times the recommended human dose based on body surface area). In rats, at 120 mg/kg/day (about 6 times the recommended human dose based on body surface area), eliglustat increased the number of late resorptions, dead fetuses and post implantation loss, reduced fetal body weight, and caused fetal cerebral variations (dilated cerebral ventricles), fetal skeletal variations (poor bone ossification) and fetal skeletal malformations (abnormal number of ribs or lumbar vertebra). Eliglustat did not cause fetal harm in rabbits at oral doses up to 100 mg/kg/day (about 10 times the recommended human dose based on body surface area). In a pre and postnatal development study in rats, eliglustat did not show any significant adverse effects on pre and postnatal development at doses up to 100 mg/kg/day (about 5 times the recommended human dose based on body surface area).

8.3 Nursing Mothers
It is not known whether CERDELGA is present in human milk. Because many drugs are present in human milk, and because of the potential for serious adverse reactions in nursing infants from CERDELGA, 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
Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use
Clinical studies of CERDELGA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Clinical experience has not identified differences in responses between the elderly and younger patients.

8.6 Renal Impairment
There is no dosage adjustment required for patients with mild renal impairment. CERDELGA has not been studied in patients with moderate to severe renal impairment or end-stage renal disease (ESRD). Use of CERDELGA in these patients is not recommended.

8.7 Hepatic Impairment
CERDELGA has not been studied in patients with hepatic impairment. Use of CERDELGA is not recommended in all stages of hepatic impairment or cirrhosis.

8.8 Poor Metabolizers
Dosing of CERDELGA 84 mg once daily has not been studied in PMs, however the predicted systemic exposures in these patients are within the range of those observed in clinical studies. Appropriate adverse event monitoring is recommended *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

10 OVERDOSAGE

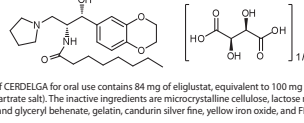
The highest eliglustat plasma concentration experienced to date occurred in a single-dose, dose escalation study in healthy subjects, in a subject taking a dose equivalent to approximately 21 times the recommended dose for GD1 patients. At the time of the highest plasma concentration (59-fold higher than normal therapeutic conditions), the subject experienced dizziness marked by disequilibrium, hypotension, bradycardia, nausea, and vomiting.

In the event of acute overdose, the patient should be carefully observed and given symptomatic and supportive treatment.

Hemodialysis is unlikely to be beneficial given that eliglustat has a large volume of distribution *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

CERDELGA (eliglustat) capsules contain eliglustat tartrate, which is a small molecule inhibitor of glucosylceramide synthase that resembles the ceramide substrate for the enzyme, with the chemical name N-{(1*R*,2*R*)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl}octanamide (2*R*,3*R*)-2,3-dihydroxysuccinate. Its molecular weight is 479.59, and the empirical formula is $C_{23}H_{36}N_2O_4 \cdot 1/2(C_4H_6O_6)$ with the following chemical structure:



Each capsule of CERDELGA for oral use contains 84 mg of eliglustat, equivalent to 100 mg of eliglustat tartrate (hemitartrate salt). The inactive ingredients are microcrystalline cellulose, lactose monohydrate, hypromellose and glyceryl behenate, gelatin, candurin silver fine, yellow iron oxide, and FD&C blue 2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Gaucher disease is caused by a deficiency of the lysosomal enzyme acid β-glucosidase. Acid β-glucosidase catalyzes the conversion of the sphingolipid glucocerebroside into glucose and ceramide. The enzymatic deficiency causes an accumulation of glucosylceramide (GL-1) primarily in the lysosomal compartment of macrophages, giving rise to foam cells or "Gaucher cells". CERDELGA is a specific inhibitor of glucosylceramide synthase (IC_{50} = 10 ng/mL), and acts as a substrate reduction therapy for GD1. In clinical trials CERDELGA reduced spleen and liver size, and improved anemia and thrombocytopenia.

In this lysosomal storage disorder (LSD), clinical features are reflective of the accumulation of Gaucher cells in the liver, spleen, bone marrow, and other organs. The accumulation of Gaucher cells in the liver, spleen, and bone marrow leads to organomegaly and skeletal disease. Presence of Gaucher cells in the bone marrow and spleen lead to clinically significant anemia and thrombocytopenia.

12.2 Pharmacodynamics

Electrocardiographic Evaluation
QTc interval prolongation was studied in a double-blind, single dose, placebo- and positive-controlled crossover study in 42 healthy subjects. Concentration-related increases were observed for the placebo-corrected change from baseline in the PR, QRS, and QTc intervals. Based on PK/PD modeling, eliglustat plasma concentrations of 500 ng/mL are predicted to cause mean (upper bound of the 95% one-sided confidence interval) increases in the PR, QRS, and QTcF intervals of 22 (26), 7 (10), and 13 (19) msec, respectively. At the highest geometric mean concentrations of 237 ng/mL following a single supratherapeutic dose tested in the thorough QT study, CERDELGA did not prolong the QT/QTc interval to any clinically relevant extent.

12.3 Pharmacokinetics

At a given dose, the systemic exposure (C_{max} and AUC) depends on the CYP2D6 phenotype. In CYP2D6 EMs and IMs, the eliglustat pharmacokinetics is time-dependent and the systemic exposure increases in a more than dose proportional manner. After multiple oral doses of 84 mg twice daily in EMs, eliglustat systemic exposure (AUC_{0-12}) increased up to about 2-fold at steady state compared to after the first dose ($AUC_{0-\infty}$). The pharmacokinetics of eliglustat in CYP2D6 PMs is expected to be linear and time-independent. Compared to EMs, the systemic exposure following 84 mg twice daily at steady state is 7- to 9-fold higher in PMs.

Absorption
In CYP2D6 EMs, median time to reach maximum plasma concentrations (t_{max}) occurs at 1.5 to 2 hours following multiple doses of CERDELGA 84 mg twice daily. The corresponding mean C_{max} values range from 12.1 to 25.0 ng/mL in EMs. The mean AUC_{tau} values range from 76.3 to 143 hr*ng/mL in EMs. The C_{max} and AUC_{tau} in one IM subject receiving multiple doses of CERDELGA 84 mg twice daily was 44.6 ng/mL and 306 hr*ng/mL, respectively. The oral bioavailability is low in EMs (<5%) following single dose of CERDELGA 84 mg due to significant first-pass metabolism.

In PMs, median t_{max} occurs at 3 hours following multiple doses of CERDELGA 84 mg twice daily. The corresponding mean C_{max} and AUC_{tau} values range from 113 to 137 ng/mL and 922 to 1057 hr*ng/mL, respectively.

Oral dosing of CERDELGA 84 mg once daily has not been studied in PMs. The predicted C_{max} and AUC_{0-24hr} in PMs using physiologically-based pharmacokinetic (PBPK) model with 84 mg once daily are 75 ng/mL and 956 hr*ng/mL, respectively.

Administration of CERDELGA with a high fat meal resulted in a 15% decrease in C_{max} but no change in AUC. Food does not have a clinically relevant effect on eliglustat pharmacokinetics.

Distribution
Eliglustat is moderately bound to human plasma proteins (76 to 83%). In the blood, it is mainly distributed in plasma and not red blood cells. After intravenous (IV) administration, the volume of distribution of eliglustat was 835 L in CYP2D6 EMs, suggesting wide distribution to tissues (CERDELGA is only for oral use).

Metabolism and Elimination
CERDELGA is extensively metabolized with high clearance, mainly by CYP2D6 and to a lesser extent CYP3A4. Primary metabolic pathways of eliglustat involve sequential oxidation of the octanoyl moiety followed by oxidation of the 2,3-dihydro-1,4-benzodioxane moiety, or a combination of the two pathways, resulting in multiple oxidative metabolites. No active metabolites have been identified.

After oral administration of 84 mg [^{14}C]-eliglustat, the majority of the administered dose is excreted in urine (41.8%) and feces (51.4%), mainly as metabolites. After 42 mg IV administration in healthy volunteers, mean (CV%) of eliglustat total body clearance was 88 L/h (8.8%) in CYP2D6 EMs (CERDELGA is only for oral use). Following multiple oral doses of CERDELGA 84 mg twice daily, eliglustat terminal elimination half-life ($T_{1/2}$) was approximately 6.5 hours in EMs and 8.9 hours in PMs.

Specific Populations
Based on population PK analysis, there was no effect of mild renal impairment on eliglustat PK. Furthermore, gender, body weight, age, and race had no clinically relevant impact on the pharmacokinetics of eliglustat.

Drug Interactions - Effect of Other Drugs on CERDELGA
In vitro, eliglustat is metabolized primarily by CYP2D6 and to a lesser extent by CYP3A4. Eliglustat is also a substrate of P-glycoprotein (P-gp).

Co-administration of CERDELGA with CYP2D6 Inhibitors
Systemic exposure (C_{max} and AUC_{tau}) of eliglustat increased 7.0-fold and 8.4-fold, respectively, following co-administration of CERDELGA 84 mg twice daily with paroxetine (a strong CYP2D6 inhibitor) 30 mg once daily in EMs (N=30), respectively.

Simulations using PBPK models suggested that paroxetine may increase the C_{max} and AUC_{tau} of eliglustat 2.1- and 2.3-fold in IMs, respectively.

Compared to paroxetine, the effects of terbinafine (a moderate inhibitor of CYP2D6) on the exposure of eliglustat in EMs or IMs were predicted to be smaller. Simulations using PBPK models suggested that terbinafine may increase the C_{max} and AUC_{tau} of eliglustat 3.8- and 4.5-fold in EMs, respectively. Both C_{max} and AUC_{tau} increased 1.6-fold in IMs.

Co-administration of CERDELGA with CYP3A Inhibitors

CYP2D6 EMs and IMs:

Following co-administration of CERDELGA 84 mg twice daily with ketoconazole (a strong CYP3A inhibitor) 400 mg once daily, the systemic exposure (C_{max} and AUC_{tau}) of eliglustat increased 4.0-fold and 4.4-fold in EMs (N=31).

Simulations using PBPK models suggested that ketoconazole may increase the C_{max} and AUC_{tau} of eliglustat 4.4- and 5.4-fold in IMs, respectively.

Compared to ketoconazole, the effects of fluconazole (a moderate inhibitor of CYP3A) on the exposure of eliglustat in EMs or IMs were predicted to be smaller. Simulations using PBPK models suggested that fluconazole may increase the C_{max} and AUC_{tau} of eliglustat 2.8- and 3.2-fold in EMs, respectively, and 2.5- to 2.9-fold in IMs, respectively.

CYP2D6 PMs:
The effect of CYP3A inhibitors on the systemic exposure of eliglustat in PMs has not been evaluated in clinical studies. Simulations using PBPK models suggest that ketoconazole may increase the C_{max} and AUC_{0-24h} of eliglustat 4.3- and 6.2-fold when co-administered with CERDELGA 84 mg once daily in PMs. Simulations using PBPK models suggested that fluconazole may increase the C_{max} and AUC_{0-24h} of eliglustat 2.4- and 3.0-fold, respectively, when co-administered with CERDELGA 84 mg once daily.

Co-administration of CERDELGA with CYP2D6 ***and*** *CYP3A inhibitors*
Simulations using PBPK models suggested that concomitant use of CERDELGA 84 mg twice daily with paroxetine and ketoconazole may increase the C_{max} and AUC_{tau} of eliglustat 16.7- and 24.2-fold in EMs, respectively. The predicted C_{max} and AUC_{tau} of eliglustat increased 7.5- to 9.8-fold in IMs, respectively.

Simulations using PBPK models suggested that concomitant use of CERDELGA 84 mg twice daily with terbinafine and fluconazole may increase the C_{max} and AUC_{tau} of eliglustat 10.2- and 13.6-fold in EMs. The predicted C_{max} and AUC_{tau} of eliglustat increased 4.2- to 5.0-fold in IMs, respectively.

Effect of CYP3A inducers on Eliglustat PK
Systemic exposures (C_{max} and AUC_{tau}) of eliglustat decreased by approximately 90% in EMs and IMs, following co-administration of CERDELGA 127 mg twice daily with rifampin (a strong CYP3A inducer) 600 mg PO once daily. The only approved dose of CERDELGA is 84 mg. Systemic exposures of eliglustat decreased by approximately 95% following co-administration of CERDELGA 84 mg twice daily with rifampin 600 mg PO once daily in PMs.

Effect of OATP (organic anion transporting polypeptide) Inhibitors on Eliglustat PK
Systemic exposures of eliglustat were similar with or without co-administration of single 600 mg IV dose of rifampin (a potent OATP inhibitor) regardless of subjects' CYP2D6 phenotypes.

Effect of P-gp Inhibitors on Eliglustat PK
The effect of P-gp inhibitors on the systemic exposure of eliglustat has not been studied clinically.

Effect of Gastric pH-Modifying Agents on Eliglustat PK
Gastric pH-modifying agents (Maalox®, Tums®, Protonix®) did not have a clinically relevant effect on eliglustat exposure.

Drug Interactions - Effect of CERDELGA on the PK of Other Drugs
Eliglustat is an inhibitor of P-gp and CYP2D6.

Following multiple doses of CERDELGA 127 mg twice daily, systemic exposures (C_{max} and AUC) to metoprolol (a CYP2D6 substrate) increased compared to metoprolol administration alone. Mean C_{max} and AUC increased by 1.7- and 2.3-fold, respectively, in EMs and by 1.2- and 1.6-fold, respectively in IMs. The only approved dose of CERDELGA is 84 mg.

Following multiple doses of CERDELGA 127 mg twice daily in EMs and IMs or 84 mg twice daily in PMs, systemic exposures (C_{max} and AUC) to digoxin (a P-gp substrate, with narrow therapeutic index) increased compared to digoxin administration alone. Mean C_{max} and AUC increased by 1.7- and 1.5-fold, respectively. The only approved dose of CERDELGA is 84 mg.

In vitro, eliglustat is a weak inhibitor of CYP3A. Repeated doses of CERDELGA 84 mg twice daily did not change the exposures to norethindrone (1.0 mg) and ethinyl estradiol (0.035 mg). Therefore, CERDELGA is not expected to impact the efficacy or safety of oral contraceptives containing norethindrone and ethinyl estradiol.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Carcinogenic potential of CERDELGA was assessed in 2-year carcinogenicity studies in rats and mice. In Sprague-Dawley rats, eliglustat was administered by oral gavage at doses up to 75 mg/kg/day in males (about 3.6 times the recommended human daily dose of 84 mg twice daily, based on body surface area) and 50 mg/kg/day in females (about 2.4 times the recommended human daily dose based on body surface area). In CD-1 mice, eliglustat was administered to males and females at up to 75 mg/kg/day (about 1.8 times the recommended human daily dose based on body surface area) via dietary admixture. Eliglustat did not produce any treatment-related neoplasms in rats or mice.

Mutagenesis
Eliglustat was negative in the Ames test, chromosome aberration test in human peripheral blood lymphocytes, mouse lymphoma gene mutation assay and *in vivo* oral mouse micronucleus test.

Impairment of Fertility
In a fertility and early embryonic development study in rats, eliglustat increased pre-implantation loss at 30 (about 1.5 times the recommended human oral dose based on body surface area) and 100 mg/kg/day (about 5 times the recommended human oral dose based on body surface area).

In mature male rats, eliglustat showed reversible adverse effects on sperm morphology, testes (germ cell necrosis), and sloughed cells in the epididymis at 200 mg/kg/day (about 10 times the recommended human oral dose based on body surface area). Similar effects on sperm were not seen in mature Cynomolgus monkeys at 72 mg/kg/day (about 7 times the recommended human oral dose based on body surface area).

14 CLINICAL STUDIES
The efficacy of CERDELGA was evaluated in three clinical trials in patients with Gaucher disease type 1.

14.1 CERDELGA in Treatment-Naïve GD1 Patients – Trial 1
Trial 1 was a randomized, double-blind, placebo-controlled, multicenter clinical study evaluating the efficacy and safety of CERDELGA in 40 treatment-naive GD1 patients 16 years of age or older (median age 30.4 years) with pre-existing splenomegaly and hematological abnormalities. Patients were required to have received no treatment with substrate reduction therapy within 6 months or ERT within 9 months prior to randomization; all but 5 patients in the study had no prior therapy. Patients were stratified according to baseline spleen volume (≤ 20 or > 20 multiples of normal [MN]) and randomized in a 1:1 ratio to receive CERDELGA or placebo for the duration of the 9-month blinded primary analysis period. The CERDELGA treatment group was comprised of IM (5%), EM (90%) and URM (5%) patients. Patients randomized to CERDELGA treatment received a starting dose of 42 mg twice daily, with a dose increase to 84 mg twice daily possible at Week 4 based on the plasma trough concentration at Week 2. The majority of patients (17 [85%]) received a dose escalation to 84 mg twice daily at Week 4, and 3 (15%) continued to receive 42 mg twice daily for the duration of the 9-month blinded primary analysis period.

The primary endpoint was the percentage change in spleen volume (in MN) from baseline to 9 months as compared to placebo. Secondary endpoints were absolute change in hemoglobin level, percentage change in liver volume (in MN), and percentage change in platelet count from baseline to 9 months compared to placebo.

At baseline, mean spleen volumes were 12.5 and 13.9 MN in the placebo and CERDELGA groups, respectively, and mean liver volumes were 1.4 MN for both groups. Mean hemoglobin levels were 12.8 and 12.1 g/dL, and platelet counts were 78.5 and 75.1 x 10^9/L respectively.

During the 9-month primary analysis period, CERDELGA demonstrated statistically significant improvements in all primary and secondary endpoints compared to placebo, as shown in Table 6.

Table 6: Change from Baseline to Month 9 in Treatment-Naïve Patients with GD1 Receiving Treatment with CERDELGA in Trial 1

	Placebo (n=20)	CERDELGA (n=20)	Difference (CERDELGA – Placebo) [95% CI]	p value*
Percentage Change in Spleen Volume MN (%)	2.3	-27.8	-30.0 [-36.8, -23.2]	<0.0001
Absolute Change in Spleen Volume (MN)	0.3	-3.7	-4.1 [-5.3, -2.9]	NA
Absolute Change in Hemoglobin Level (g/dL)	-0.5	0.7	1.2 [0.6, 1.9]	0.0006
Percentage Change in Liver Volume MN (%)	1.4	-5.2	-6.6 [-11.4, -1.9]	0.0072
Absolute Change in Liver Volume (MN)	0.0	-0.1	-0.1 [-0.2, 0.0]	NA
Percentage Change in Platelet Count (%)	-9.1	32.0	41.1 [24.0, 58.2]	<0.0001
Absolute Change in Platelet Count (x 10^9/L)	-7.2	24.1	31.3 [18.8, 43.8]	NA

MN = Multiples of Normal, CI = confidence interval, NA = Not applicable
*Estimates and p-value are based on ANCOVA model that includes treatment group, baseline spleen severity group (≤20MN, >20MN) and baseline parameter value.

In an uncontrolled study of treatment naïve GD1 patients, improvements in spleen and liver volume, hemoglobin level, and platelet count continued through the 4 year treatment period.

14.2 Patients Switching from Enzyme Replacement Therapy to CERDELGA – Trial 2
Trial 2 was a randomized, open-label, active-controlled, non-inferiority, multicenter clinical study evaluating the efficacy and safety of CERDELGA compared with imiglucerase in 159 treated GD1 patients (median age 37.4 years) previously treated with enzyme replacement therapy (≥3 years of enzyme replacement therapy, dosed at 30-130 U/kg/month in at least 6 of the prior 9 months) who met pre-specified therapeutic goals at baseline. Pre-specified baseline therapeutic goals included: no bone crisis and free of symptomatic bone disease within the last year; mean hemoglobin level of ≥ 11 g/dL in females and ≥ 12 g/dL in males; mean platelet count ≥ 100,000/mm^3; spleen volume < 10 times normal and liver volume < 1.5 times normal.

Patients were randomized 2:1 to receive CERDELGA or imiglucerase for the duration of the 12-month primary analysis period. Seventy-five percent of patients randomized to CERDELGA were previously treated with imiglucerase; 21% with velaglucerase alfa and 4% were unreported. Patients randomized to CERDELGA treatment received a starting dose of 42 mg twice daily, with dose increases to 84 mg twice daily and 127 mg twice daily possible at Weeks 4 and 8 based on plasma trough concentrations of CERDELGA at Weeks 2 and 6, respectively. The percentage of patients receiving the 3 possible CERDELGA doses was: 42 mg twice daily (20%), 84 mg twice daily (32%) and 127 mg twice daily (48%). The CERDELGA treatment group was comprised of PM (4%), IM (10%), EM (80%) and URM (4%) patients.

At baseline, mean spleen volumes were 2.6 and 3.2 MN in the imiglucerase and CERDELGA groups, respectively, and liver volumes were 0.9 MN in both groups. Mean hemoglobin levels were 13.8 and 13.6 g/dL, and platelet counts were 192 and 207 x 10^9/L, respectively.

The primary composite endpoint required stability in all four component domains (hemoglobin level, platelet count, liver volume, and spleen volume) based on changes between baseline and 12 months. Stability was defined by the following pre-specified thresholds of change: hemoglobin level <1.5 g/dL decrease, platelet count < 25% decrease, liver volume <20% increase and spleen volume <25% increase. The percentages of patients meeting the criteria for stability in the individual components of the composite endpoint were assessed as secondary efficacy endpoints.

CERDELGA met the criteria to be declared non-inferior to imiglucerase in maintaining patient stability. After 12 months of treatment, the percentage of patients meeting the primary composite endpoint was 84.8% for the CERDELGA group compared to 93.6% for the imiglucerase group. The lower bound of the 95% CI of the 8.8% difference, -17.6%, was within the pre-specified non-inferiority margin of -25%. At Month 12, the percentages of CERDELGA and imiglucerase patients respectively, who met stability criteria for the individual components of the composite endpoint were: hemoglobin level, 94.9% and 100%; platelet count, 92.9% and 100%; spleen volume, 95.8% and 100%; and liver volume, 96.0% and 93.6%. Of the patients who did not meet stability criteria for the individual components, 12 of 15 CERDELGA patients and 3 of 3 imiglucerase patients remained within therapeutic goals for GD1.

Mean changes from baseline in the hematological and visceral parameters through 12 months of treatment are shown in Table 7. There were no clinically meaningful differences between groups for any of the four parameters.

Table 7: Mean Changes from Baseline to Month 12 in Patients with GD1 Switching to CERDELGA in Trial 2

	Imiglucerase (N=47) Mean [95% CI]	CERDELGA (N=99) Mean [95% CI]
Percentage Change in Spleen Volume MN (%)*	-3.0 [-6.4, 0.4]	-6.2 [-9.5, -2.8]
Absolute Change in Spleen Volume (MN)*	-0.1 [-0.2, 0.0]	-0.2 [-0.3, -0.1]
Absolute Change in Hemoglobin Level (g/dL)	0.0 [-0.2, 0.2]	-0.2 [-0.4, -0.1]
Percentage Change in Liver Volume MN (%)	3.6 [0.6, 6.6]	1.8 [-0.2, 3.7]
Absolute Change in Liver Volume (MN)	0.0 [0.0, 0.1]	0.0 [0.0, 0.0]
Percentage Change in Platelet Count (%)	2.9 [-0.6, 6.4]	3.8 [0.0, 7.6]
Absolute Change in Platelet Count (x 10^9/L)	6.0 [-0.9, 13.0]	9.5 [1.4, 17.6]
Patients Stable for 52 Weeks, n (%) (Composite Primary Endpoint)	44 (93.6)	84 (84.8)

MN = Multiples of Normal, CI = confidence interval
* Excludes patients with a total splenectomy.

16 HOW SUPPLIED/STORAGE AND HANDLING

CERDELGA is supplied as 84 mg hard gelatin capsules, with a pearl blue-green opaque cap and pearl white opaque body imprinted with "GZ02" in black.

CERDELGA 84 mg capsules are supplied as:

NDC-58468-0220-1 – Carton containing 4 packs of capsules (56 capsules total). Each pack is composed of 1 blister card of 14 capsules and a cardboard wallet.

NDC-58468-0220-2 – Carton containing 1 pack of capsules (14 capsules total). Each pack is comprised of 1 blister card of 14 capsules and a cardboard wallet.

Store at 68 °F - 77 °F (20 °C - 25 °C) with excursions permitted between 59 °F and 86 °F (15 °C to 30 °C) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Drug Interactions
Advise patients to discuss all the medications they are taking, including any herbal supplements or vitamins with their healthcare provider *[see Contraindications (4) and Drug Interactions (7)]*.

ECG Changes and Potential for Cardiac Arrhythmias
Advise patients to inform their healthcare provider of the following: history of congestive heart failure; recent acute myocardial infarction; bradycardia; heart block; ventricular arrhythmia; and long QT syndrome *[see Warnings and Precautions (5.2)]*.

Advise patients to inform their healthcare provider if they develop new symptoms such as palpitations, fainting, and dizziness.

Administration Instructions
Advise patients:
- Swallow capsules whole, preferably with water, and do not crush, dissolve, or open the capsules.
- CERDELGA can be taken with or without food.
- If a dose of CERDELGA is missed, take the prescribed dose at the next scheduled time; do not double the next dose.
- Avoid consumption of grapefruit or its juice.
- For patients currently treated with imiglucerase, velaglucerase alfa, or taliglucerase alfa, CERDELGA may be administered 24 hours after the last dose of the previous enzyme replacement therapy (ERT).

Manufactured by:
Genzyme Ireland, Ltd., IDA Industrial Park, Old Kilmeaden Road, Waterford, Ireland.

MEDICATION GUIDE
CERDELGA™ (sir-DEL-guh)
(eliglustat) capsules

What is the most important information I should know about CERDELGA?

CERDELGA can affect the way other medicines work and other medicines can affect how CERDELGA works. Using CERDELGA with other medicines or herbal supplements may cause an increased risk of side effects.
Especially tell your doctor if you take:
- St. John's Wort (Hypericum perforatum)
- Medicine for:
  - Fungal infections
  - Tuberculosis
  - Seizures
  - Heart conditions or high blood pressure
  - Depression or other mental health problems

If you take any medicines for the conditions listed above, your doctor may need to prescribe a different medicine, change your dose of other medicines, or change your dose of CERDELGA. Tell your doctor about any new medicines before you start taking them.

What is CERDELGA?

CERDELGA is a prescription medicine used for the long-term treatment of Gaucher disease type 1 (GD1) in adults.
CERDELGA is not used in certain people with Gaucher disease type 1. Your doctor will perform a test to make sure that CERDELGA is right for you.
It is not known if CERDELGA is safe and effective in children.

What should I tell my doctor before taking CERDELGA?

Before taking CERDELGA, tell your doctor about all of your medical conditions, including if you:
- have heart problems, including a condition called long QT syndrome
- have a history of a heart attack
- have kidney or liver problems
- are pregnant or planning to become pregnant. It is not known if CERDELGA will harm your unborn baby.
- are breastfeeding or planning to breastfeed. It is not known if CERDELGA passes into your breast milk. You and your doctor will decide if you should take CERDELGA or breastfeed. You should not do both.

Tell your doctor about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. See **"What is the most important information I should know about CERDELGA?"**

How should I take CERDELGA?

- Take CERDELGA exactly as your doctor tells you to take it.
- Your doctor may change your dose if needed.
- Take CERDELGA capsules whole, preferably with water. Do not open, crush, or dissolve capsules before swallowing.
- CERDELGA can be taken with or without food.
- If you miss a dose of CERDELGA, take the next dose at the usual time. Do not take two doses of CERDELGA at the same time.
- If you take too much CERDELGA, call your doctor or go to the nearest hospital emergency room right away.

What should I avoid while taking CERDELGA?

Avoid eating or drinking grapefruit products while taking CERDELGA. Grapefruit products can increase the amount of CERDELGA in your body.

What are the possible side effects of CERDELGA?

See **"What is the most important information I should know about CERDELGA?"**
- **CERDELGA, used with certain other medicines, may cause changes in the electrical activity of your heart (ECG changes) and irregular heart beat (arrhythmias).** Tell your doctor if you have new symptoms such as palpitations, fainting, or dizziness.

The most common side effects of CERDELGA include: tiredness, headache, nausea, diarrhea, and pain in the arms, legs, back, or stomach (abdomen).
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 CERDELGA.
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 CERDELGA?

- Store CERDELGA at room temperature between 68°F to 77 °F (20°C to 25 °C).
- Keep CERDELGA and all medicines out of reach of children.

General information about the safe and effective use of CERDELGA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use CERDELGA for a condition for which it was not prescribed. Do not give CERDELGA 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 CERDELGA that is written for health professionals.
For more information, go to www.cerdelga.com or call 1-800-745-4447.

What are the ingredients in CERDELGA?

Active ingredient: eliglustat
Inactive ingredients: microcrystalline cellulose, lactose monohydrate, hypromellose, glyceryl behenate, gelatin, candurin silver fine, yellow iron oxide, and FD&C blue 2

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: August 2014
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